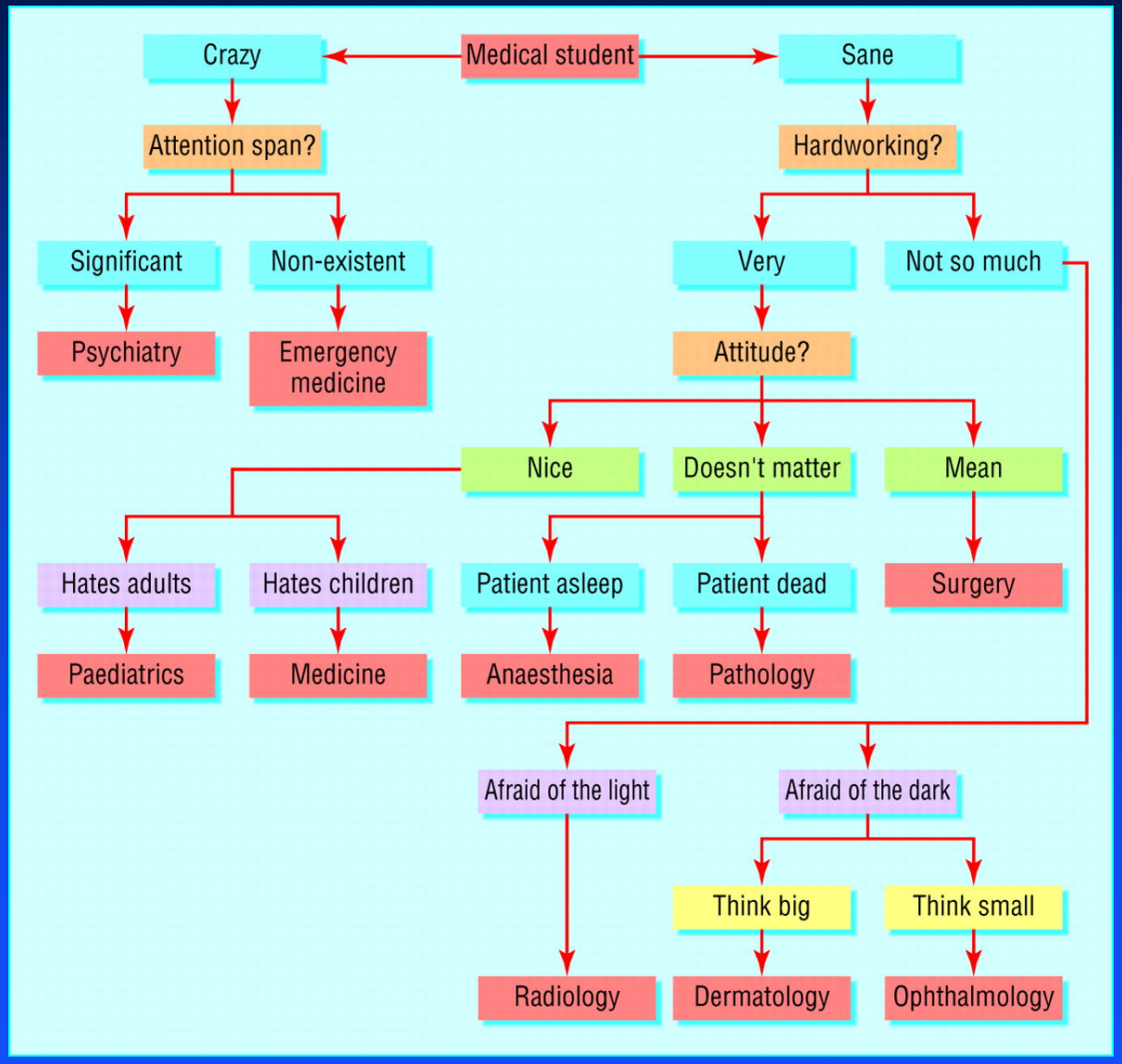
Endocrinology Introductory Lectures

What do You Want to Become?



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

Gland/Product/Class

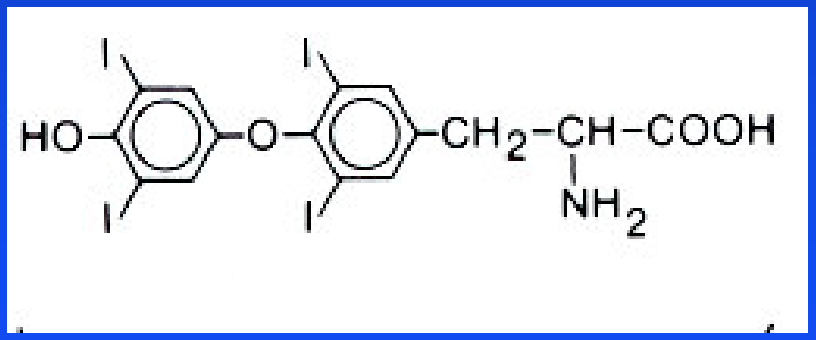
- Posterior Pituitary (Neurohypophysis)
  - Antidiuretic Hormone (ADH)
  - Peptide

Gland/Product/Class

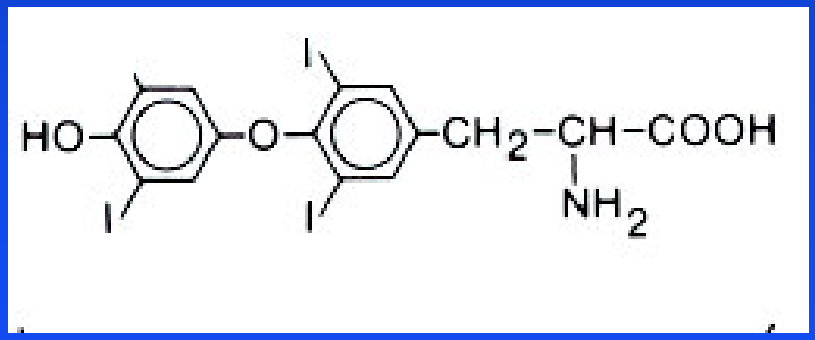
- Hypothalamus
  - Gonadotropin Releasing Hormone (GnRH)
  - Growth Hormone Releasing Hormone (GHRH)
  - Thyrotropin Releasing Hormone (TRH)
  - Corticotropin Releasing Hormone (CRH)
  - Somatostatin
  - Prolactin Inhibiting Factor (Dopamine)
  - Peptide/Protein

Gland/Product/Class

- Thyroid
  - Thyroxine (T4) — Amine
  - Triiodothyronine (T3)
  - Calcitonin — Protein



T4



T3

Gland/Product/Class

- Parathyroid
  - Parathyroid Hormone (PTH) Protein

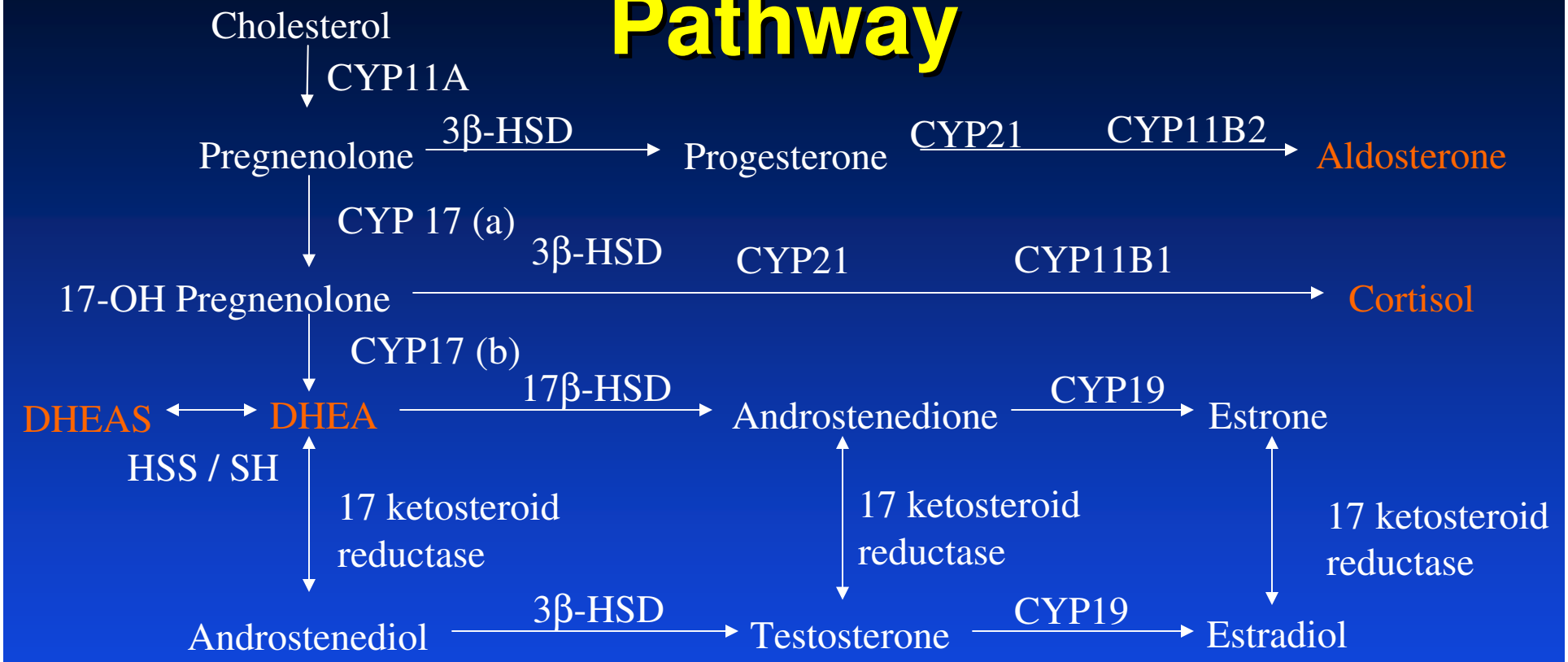
Gland/Product/Class

- Pancreas
  - Insulin — Peptide/Protein
  - Glucagon
  - Somatostatin

Gland/Product/Class

- Adrenal Cortex
  - Cortisol Steroid
  - Aldosterone
  - Adrenal “androgens” - DHEA

Simplified Steroid Synthesis Pathway



Simplified steroid synthesis pathway. CYP 11A: 20, 22 Hydroxylase, 20, 22- desmolase; CYP11B1: 11β hydroxylase; CYP11B2: 11β hydroxylase, 18 – hydroxylase and 18 – oxidase; CYP17 (a): 17α Hydroxylase (catalysed by P450 $_{c17}$); CYP17 (b): 17, 20 Lyase (catalysed by P450 $_{c17}$); CYP19: Aromatase; CYP21: 21 Hydroxylase; 3β-HSD: 3β-Hydroxysteroid dehydrogenase; 17β-HSD: 17β-Hydroxysteroid dehydrogenase; HSS: 3β Hydroxysteroid sulphotransferase, SH: sulphohydrolayse.

Gland/Product/Class

- Adrenal Medulla
  - Epinephrine — Amine
  - Norepinephrine
  - Dopamine

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

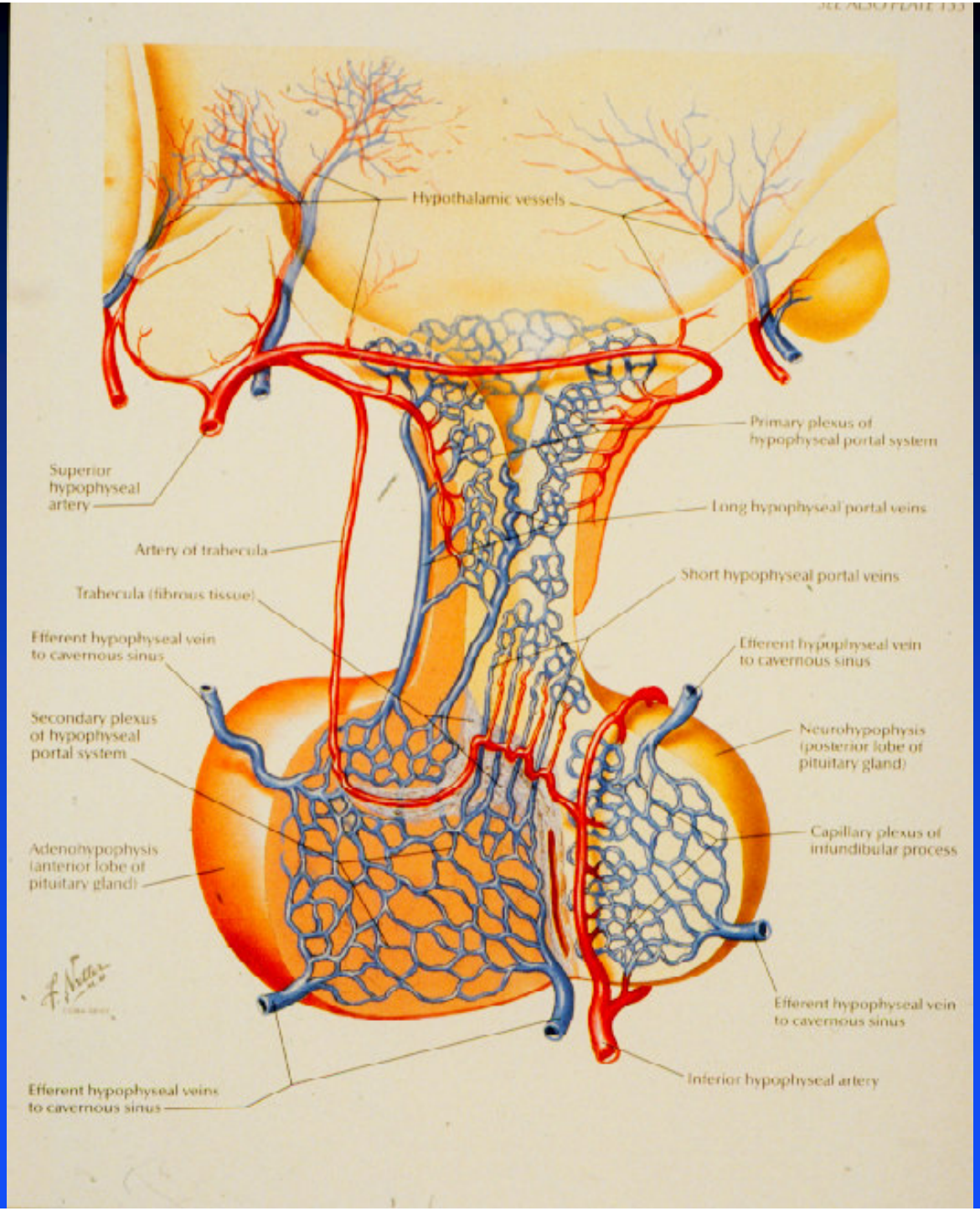
- Polypeptides:
  - LH/FSH, TSH, hCG, ACTH, PTH, Insulin, Glucagon, Somatostatin, TRH, GnRH, IGF I & II, and others
- Amino acid derivatives:
  - Thyroxine, Triiodothyronine, Catecholamines (Epinephrine, Norepinephrine, Dopamine), Serotonin, Histamine

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} M) for peptide hormones
- Must be directed to site of action very specifically-targeting


Hypothalamic vessels
Primary plexus of hypophyseal portal system
Superior hypophyseal artery
Long hypophyseal portal veins
Artery of trabecula
Short hypophyseal portal veins
Trabecula (fibrous tissue)
Efferent hypophyseal vein to cavernous sinus
Efferent hypophyseal vein to cavernous sinus
Secondary plexus of hypophyseal portal system
Neurohypophysis (posterior lobe of pituitary gland)
Capillary plexus of infundibular process
Adenohypophysis (anterior lobe of pituitary gland)
Efferent hypophyseal vein to cavernous sinus
Inferior hypophyseal artery
Efferent hypophyseal veins to cavernous sinus

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)

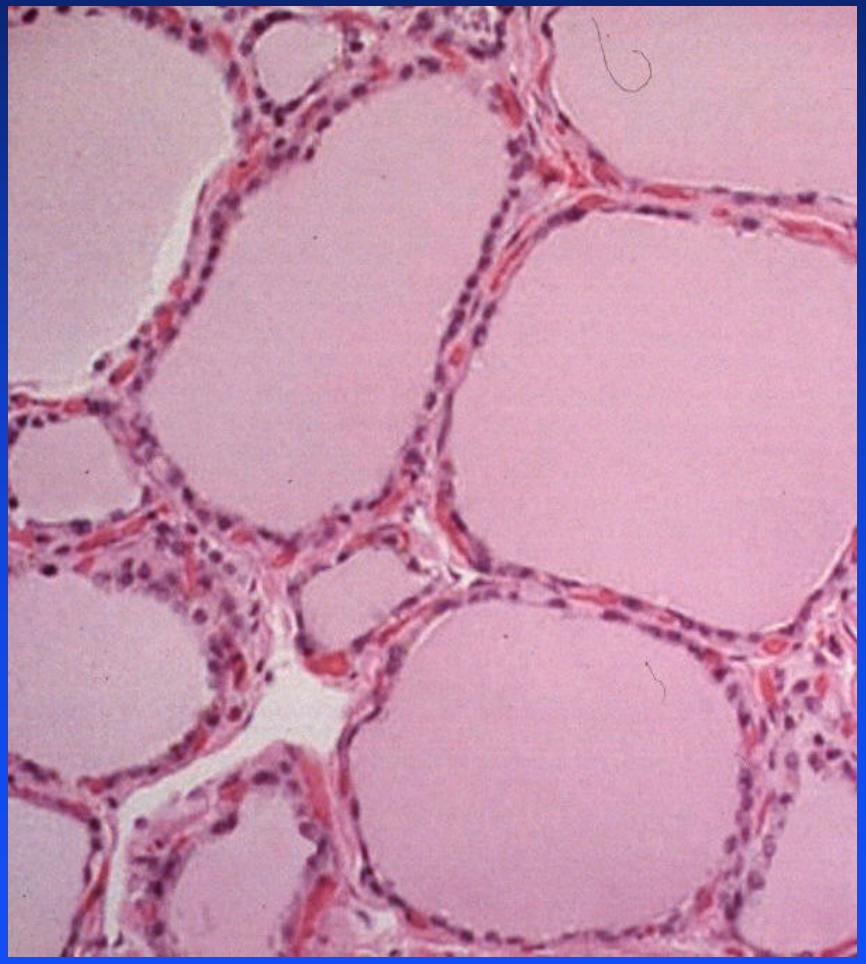
Hormone Biosynthesis

- 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 H_2O 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 α and β 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

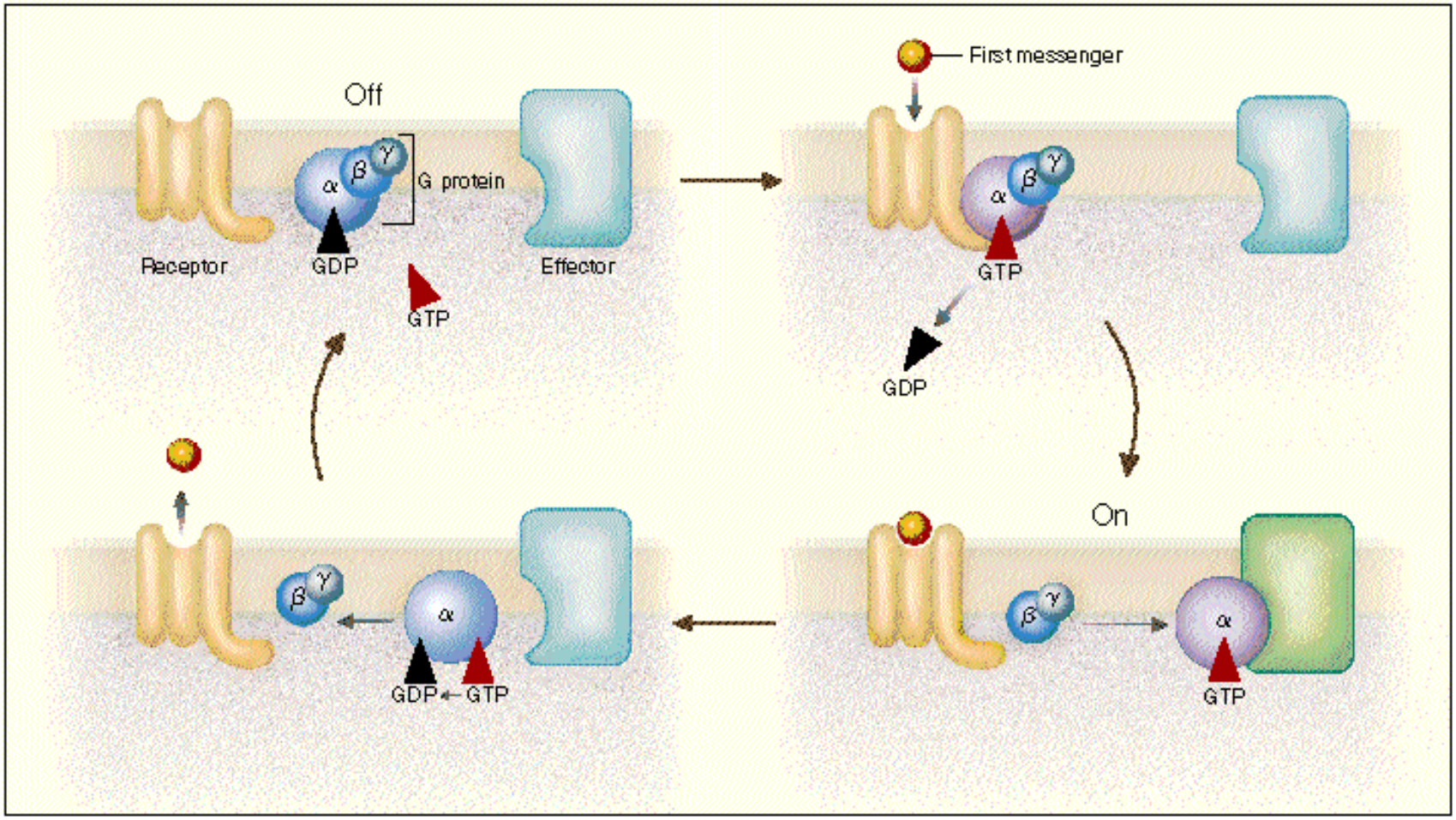
Hormone Receptors

- 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

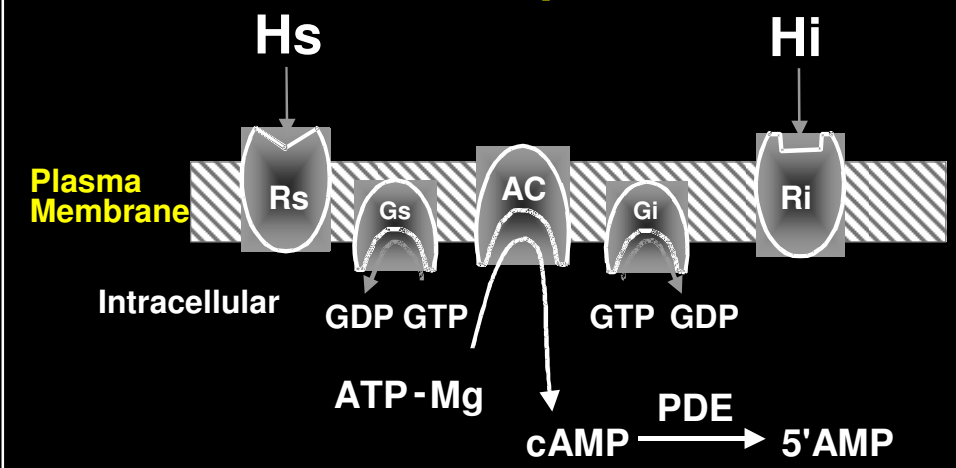
Hormone Receptors

- Membrane Receptors:
  - G-protein coupled
  - Non G-protein coupled
- Nuclear Receptors:
  - Steroid hormone receptor “superfamily”

G-protein Coupled



G-Protein Linked Membrane Receptors



Protein Kinase

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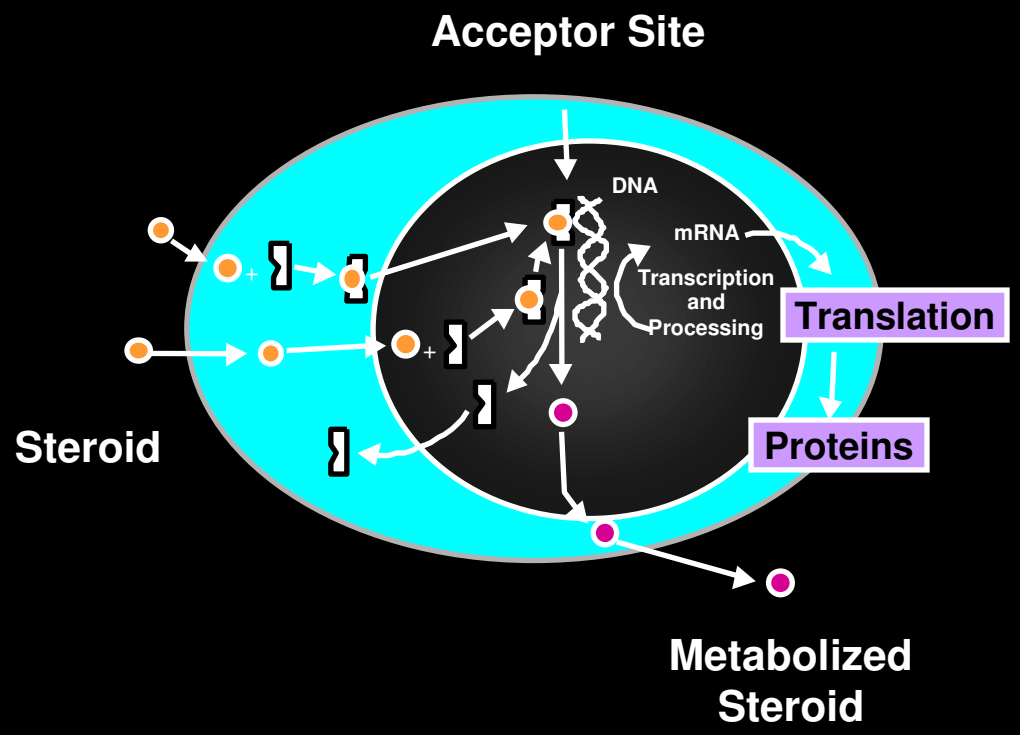
Phosphorylated Proteins

↓

Physiologic Effect(s)

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

Nuclear Receptors



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

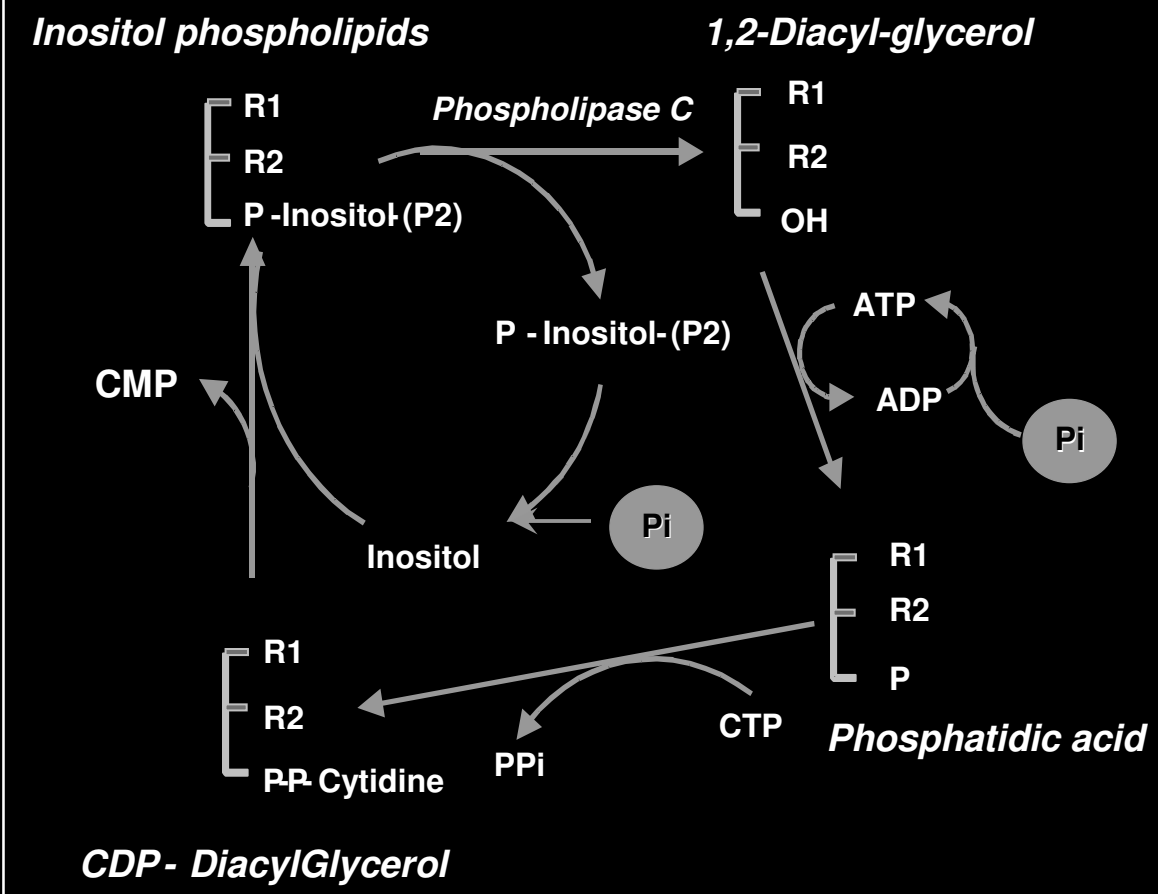
Receptor Concentrations

- "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



Regulation of Hormone Secretion

- All hormones are under some type of feedback control
- Secretory 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?