Endocrinology

Course	Essential Protein Structure and Function
Confidence	Confident
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Pituitary

The endocrine system

A collection of glands that secrete chemical messages – hormones, to maintain homeostasis in parallel with the nervous system. Hormones passed through the blood via circulation to arrive at a target organ, which has cells possising the appropriate receptor.

- Maintains homeostasis and long-term control using chemical signals.
- Works in parallel with the nervous system to control homeostasis.
- More than 50 human hormones have been identified; all act by binding to receptor molecules

Hormones

- Grouped into three classes based on their biochemical structure
  - Peptides
  - Amines
  - Steroids
- Peptides (most hormones)
  - Short chains of amino acids
  - Secreted by the pituitary, parathyroid, heart, stomach, liver, and kidneys.
- Amines

    - Derived from the amino acid tyrosine and are secreted from the thyroid and the adrenal medulla
        - Thyroid hormone, adrenaline?
- Steroids
    - Lipids derived from cholesterol
    - Steroid hormones are secreted by the gonads, adrenal cortex, and placenta
    - Testosterone - male sex hormone
    - Oestradiol - responsible for many female sex characteristics

Mechanisms of hormone action

- The endocrine system acts by releasing hormones that in turn trigger actions in specific target cells
- Receptors on target cell membranes **only bind to one type of hormone**
- The binding hormone changes the conformation of the receptor causing the response to the hormone
- Circulating hormones: Hormones secreted by endocrine cells and reaches distant target cells possessing the receptors via circulation
- Local hormones
    - Paracrines: Hormones bind to paracrine receptors on nearby target cells
    - Autocrines: Hormones bind to the autocrine receptors on the same cell
    - More subtle changes modified by less hormone production
    - Usually within organs such as brain

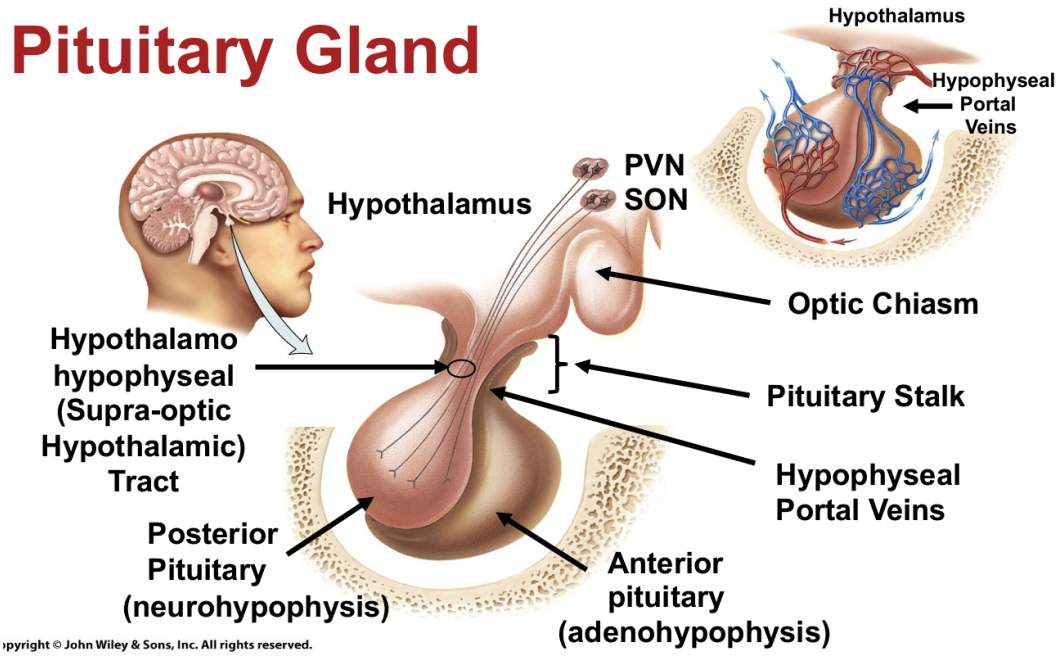
1. Non-Steroidal signalling
    - Non-steroidal hormones are water soluble. They do not enter the cell but bind to plasma membrane receptors, generating a chemical signal (second messengers) inside the target cell.
    - Surface receptors relay extracellular signal to intracellular
    - 5 different second messengers have been identified (e.g. cAMP, DAG, IP3)

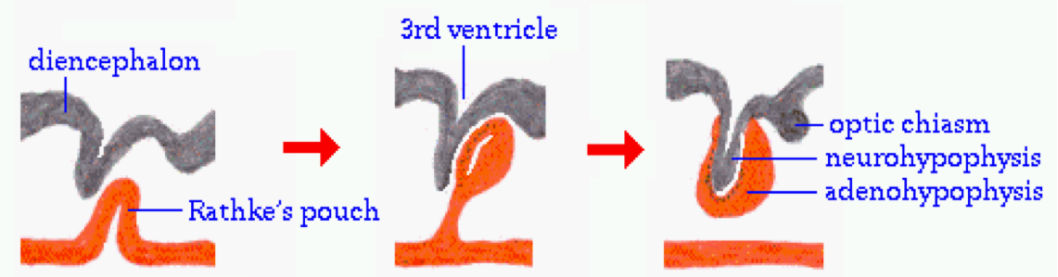
- Second messengers activate other intracellular chemicals to produce the target cell response
    - Amplification
        - One receptor may activate multiple first messengers, which may then activate multiple second messengers

2. Steroid signalling
    - Steroid hormones pass through the plasma membrane and act in a 2 step process
        a. Once inside the cell, steroid hormones bind to the nuclear membrane receptors, producing an activated hormone-receptor complex
        b. The complex binds to DNA and activates specific genes, increasing its expression and thus protein production
    - Usually slow but long-term effects

Endocrine-related Problems

- Overproduction of a hormone
- Underproduction of a hormone
    - Can be directly measured
- Non-functional receptors that cause target cells to become insensitive to hormones
    - Lots of hormone measured but no effects elicited, could be due to:
        - Lack of receptor functionality
        - Mutated hormone





- Posterior pituitary is a down-growth from brain
- Anterior pituitary is an up-growth from mouth

Posterior pituitary

- Vasopressin (AVP) = anti-diuretic hormone (ADH)
  - Effects on blood vessels - vasoconstriction via V1R, thus cause increase in BP
    - Activated by blood volume or pressure drop - baroreceptors in cardiovascular system
  - Effects on kidney function - insertion of AQP2 into the cell membrane and increase water retention
  - Also called arginine vasopressin to distinguish it from ADH produced by other species
  - Net effect is to aid water reabsorption by the kidney

- Oxytocin (OT)
  - Stimulates milk ejection
  - Stimulates uterine smooth muscle contraction at birth
  - Establishment of maternal behavior
- Synthesised in cell bodies of magnocellular neurons - Paraventricular Nucleus (PVN) and the Supraoptic Nucleus (SON)
- Axonal transported from hypothalamus to posterior pituitary
- OT differs from AVP in 2 of the 9 amino acids
- Both hormones are packaged into granules and secreted along with carrier proteins called neurophysins

Anterior pituitary

Cell population	Secreted hormone	Endocrine action
Thyrotrophs	TSH (thyroid-stimulating hormone)	Stimualtes synthesis and secretion of thyroid hormones
Gonadotrophs	Gonadotrophins: LH (luteinizing hormone) & FSH (follicle-stimulating hormone)	Stimulate steroid biosynthesis and germ cell maturation in the gonads
Corticotrophs	ACTH (adrenocorticotrophic hormone)	Stimulates steroid biosynthesis in adrenal cortex
Somatotrophs	Somatotrophin = GH (growth hormone)	Stimulates growth (via insulin-like growth factor, IGF-1)
Lactotrophs	Prolactin	Stimulates lactation

TSH, LH &FSH

- Heterodimeric glycoproteins
- Common alpha subunit
- Specfic beta subunits (TSHbeta, LHbeta, FSHbeta)

ACTH

- 39 amino acid fragment of POMC (cleavage product)

GH & PRL

- 190 amino acid peptides - internal di-S bonds
- Homologous receptors

Intermediate Lobe

- The intermediate lobe shows considerable variation in size among species
- Small in humans, larger in species such as amphibians, where **melanocyte-stimulating hormone** is the predominant hormone secreted, e.g. chameleon, skin colour changes

Control of anterior pituitary function

Hypothalamic factors

- Synthesis and secretion of anterior pituitary hormones can be under control of
    - Hypothalamic releasing hormones (neural control of anterior pituitary)
    - Hypothalamic inhibitory factors
- Synthesised in parvicellular neurons - secreted at median eminence of third ventricle

Hypothalamic-releasing hormones

- TRH (3aa) - stimulates thyrotrophin (TSH)
- GnRH (10aa) - stimulates gonadotrophin (LH&FSH)
- CRH (41aa) - stimulates corticotrophins (ACTH)
- GHRH (44aa) - stimulates GH

a. Increase synthesis and secretion via Gs protein (AC-cAMP, PKA, CREB pathway)

   e.g. CRH & GHRH

b. Increase intracellular Ca via PLC pathway (Gq protein)

   e.g. GnRH & TRH (similar structure of anterior pituitary hormone)

Hypothalamic-inhibitory hormones

- SRIF (somatostatin, 40aa) - inhibits GH

Dual control of GH Secretion

- GHRH stimulates GH secretion which stimulates IGF-1 by the liver and growth
- IGF-1 inhibit anterior pituitary secretion of GH and hypothalamus secretion of GHRH via negative feedback loop
- Somatostatin secreted by the hypothalamus and pancreas inhibit GH secretion
- Stress inhibit GHRH secretion

Exception

- Rule: anterior pituitary stimulated by hypothalamic releasing hormones (& may be suppressed by hypothalamic inhibitory factors)
- BUT: **no key stimulus for prolactin synthesis / secretion**
- Appears to be under dominant negative control by dopamine (from arcuate nucleus)
    - Dopamine **inhibit** prolactin synthesis

Negative feedback loops

- Hypothalamic-pituitary-thyroid (HPT) axis
    - TRH stimulates TSH stimulates Thyroid hormones (T4+T3) which inhibits the formers
- Hypothalamic-pituitary-gonadal (HPG) axis
    - GnRH stimulates LH (+FSH) stimulates progesterone/testosterone/oestradiol and inhibits
- Hypothalamic-pituitary-adrenal (HPA) axis
    - CRH stimulates ACTH stimulates cortisol and inhibits

Positive feedback spirals and hormone secretion

Suckling reflex

- The act of nursing or suckling is relayted within a few milliseconds to the brain via a spinal reflex arc (i.e. neural part of pituitary)
- These signals impinge on oxytocin-secretin neurons, leading to release of oxytoxin from posterior pituitary

Fergusson reflex

- The stimulation of the reproductive tract as an infant is born send signals to increase oxytocin release to increase muscle contraction until the birthing process is complete

LH surge (involving hypothalamic-pituitary-gonadal (HPG) axis)

- The positive feedback effect of oestrogen is the mechanism by which the GnTH cells of the hypothalamus and pituitary gonadotrophs produce surges in the secretion of GnRH and gonadotrophins LH&FSH, respectively, that lead to ovulation

▼ **Mechanism of the LH Surge**

1. **Rising Estrogen Levels**: During the follicular phase of the menstrual cycle, developing follicles in the ovaries secrete increasing amounts of estrogen. As a dominant follicle matures, it produces higher levels of estrogen.
2. **Switch from Negative to Positive Feedback**: Typically, estrogen exerts negative feedback on the hypothalamus and pituitary, inhibiting the release of GnRH and, consequently, LH and FSH. However, when estrogen levels reach a critical threshold and remain elevated for a sustained period, usually mid-cycle, the feedback mechanism switches from negative to positive. This positive feedback stimulates the hypothalamus and anterior pituitary to increase the release of GnRH and LH, respectively.
3. **LH Surge**: The surge in GnRH from the hypothalamus triggers a dramatic and rapid increase in LH secretion by the anterior pituitary. This LH surge leads to several critical ovulatory events within the ovary: it causes the mature follicle to rupture, releasing the ovum (egg), and initiates the transformation of the ruptured follicle into the corpus luteum, which produces progesterone to prepare the endometrium for potential implantation.

Pituitary dysfunction

Hyposecretion of anterior pituitary hormones

- Anterior pituitary cells are sensitive to irradiation (i.e., radiation) - particular somatotrophs
    - Thus less growth
- Hyposecretion of individual anterior pituitary hormones - rare due to mutation of the gene, promoter etc.
    - Only after at birth as in utero growth not regulated by hormone

Hypersecretion of anterior pituitary hormones

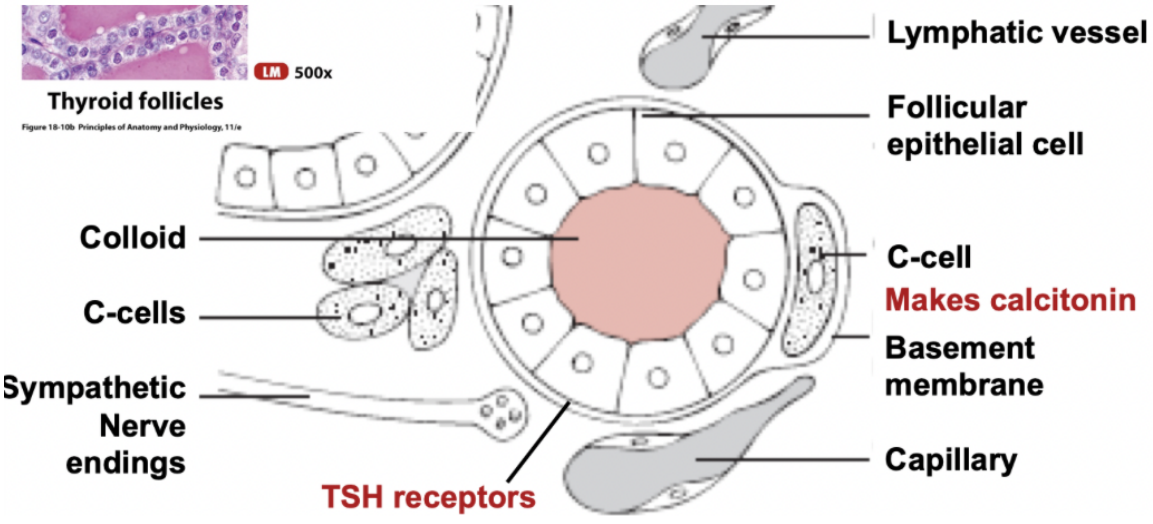
- Functional pituitary tumours - rare
- GH hypersecretion
    - Gigantism (in infancy)
        - Excess height
    - Acromegaly (in adulthood)
        - Excess catilage growth, hand, feet, etc.
- ACTH hypersecretion
    - From pituitary corticotrophs - Cushing’s disease
        - Hypertension
        - Moon face
        - Obesity
        - Abdominal striae
        - Muscle wasting in the extremities
    - Excess cortisol production

Thyroid Axis

Thyroid hormone axis

- Thyrotrophin releasing hormone (TRH) stimualtes secretion of thyroid stimulating hormone (TSH), which stimulates production of thyroid hormone (T3 &T4)
- Thyroid hormone inhibits TSH and TRH via negative feedback
- Thyroid hormones are regulated by hypothalamic production of neuropeptides as other endocrine axes, thyroid releasing hormone (TRH)
    - TRH is released from the paraventricular cells and released into the median eminence of hypothalamus, where it enters the fenestrated portal capillaries, down through the pituitary stalk into the anterior pituitary
    - TRH acts on thyrotrophs, which releases TSH (thyroid stimulating hormone) into the circulation
    - TSH acts on epithelial follicular cells in thyroid
        - A collection of protein (extracellular) with cells surrounding them
        - Blood vessels and nerves surround the follicles
    - T3 and T4 secreted by the follicular cells then act on the axis via negative feedback on TRH and TSH
        - T4 (precursor) normal plasma concentration: 60-150 nanomolar (~10^-7 M)
        - T3 (active): 1.2-2.9 nanomolar (~10^-9 M)

▼ Thyroid Morphology



- The functional unit is the follicle, each bounded by a basement membrane.
- Every follicle consists of an epithelial layer of follicular cells surrounding a central colloid-filled cavity.
- When the thyroid is highly active, the follicles contain little colloid and the follicular epithelial cells have a tall columnar appearance.
    - During periods of relative inactivity, however, the follicles fill with colloid and the epithelial cells then assume a flattened, cuboidal appearance.
- Microvilli on the luminal (colloid) surface of the follicular cells
- Parafollicular cells (C-cells) lie scattered between the follicles. These cells secrete calcitonin and do not come into contact with the follicular colloid.

Thyroid hormone transport

- Thyroid hormones are **hydrophobic** and thus poorly soluble in water, and more than 99% of the T3 and T4 circulating in blood is **bound to carrier proteins**
- The principle carrier of thyroid hormones is **thyroxine-binding globulin**, a glycoprotein synthesized in the liver. Two other carriers of import are **thyroxine binding prealbumin** (transthyrein) and **albumin**.
    - Carrier proteins allow maintenance of a stable pool of thyroid hormones from which the active, free hormones are released for uptake by target cells
- **Conversion of T4 to T3** is observed in the **cytosol** after transport into the target cell
- There is a high blood flow through the thyroid gland
    - 4-6 ml/min/g thyroid tissue, i.e. twice of the kidney
    - The high rate is important for both the delivery of iodine and TSH and secretion of T3 and T4

Synthesis and Secretion

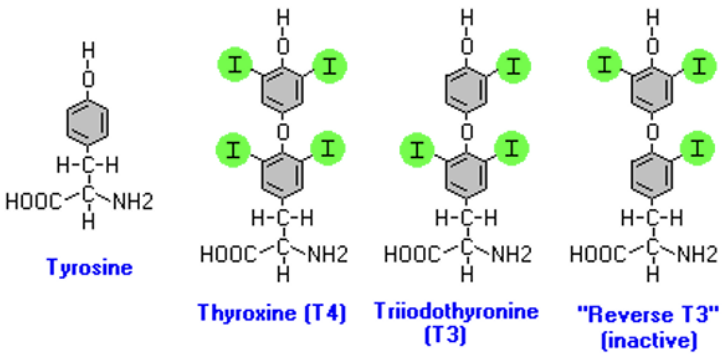
- Three major steps

    - Production and accumulation of the raw materials
        - Thyroid hormones are the only substances in the body that contain iodine; thyroid gland is the only tissue with iodide transporter (apart from those in GI tract)
        - Dark green leafy vegetables (e.g. seaweed)
    - Synthesis of the hormones on a scaffold of precursors
        - Scaffold - a protein called thyroglobulin
        - Follicular cells produce and secrete thyroglobulin into the colloid
        - Thyroglobulin incorporates iodine atoms into tyrosine residues
        - Contained within the colloid are tyrosine residues held to the thyroglobulin molecules by peptide linkages, the iodinated protein is stored within the lumen of the thyroid follicle and can last for weeks/months
        - Synthesis of thyroid hormones is carried out by the enzyme **thyroid peroxidase** catalyses:
            - Iodination of tyrosine on thyroglobulin "organification of iodine"
            - Synthesis of T4 or T3 from two iodotyrosines (T1&T2)
    - Release of the free hormones from the scaffold and secretion into blood
        - Thyroglobulin is hydrolysed before T3 and T4 are released into circulation
- **TSH stimulates each of these processes**.
- Binding of TSH to its receptors on thyroid epithelial cells stimulates the synthesis of:
    - Iodine transporter - raw material accumulation
    - Thyroid peroxidase (TPO) - linking iodine to tyrosine
    - Thyroglobulin - backbone protein
- Note: the magnitude of the TSH signal sets the rate of endocytosis of colloid - high concentrations of TSH lead to faster rates of endocytosis,

and thus release into the circulation. Conversely, when TSH levels are low, rates of thyroid hormone synthesis and release diminish.

Chemistry of thyroid hormones

- Thyroid hormones are derivatives of the amino acid tyrosine bound covalently to iodine
- Thyroid biosynthesis takes place within the structure of thyroglobulin in the colloid space between follicular epithelial cells of the thyroid. This process is called iodination / organification.
- Thyroid hormones are basically two tyrosine linked together with the critical addition of iodine at 3 or 5 positions on the aromatic rings
    - The number and position of the iodine is important



- T3: outer ring 3 and inner ring 3,5,
    - D1 and D2 remove 5′ position
- Reverse T3: outer ring 3,5, inner ring 3

- Thyroxine (T4) has longer half life than triiodothyronine (T3)
    - The body tends to circulate a higher level of longer half life T4
- Several other iodinated molecules are generated that have little or no biological activity; so called reverse T3 or T2
- T4 regarded as a pro-hormone for T3
    - T4 can be activated either within the thyroid gland or at target tissue
- Local control of thyroid hormone
    - Because T3 and T4 has long half life (for days), local control by peripheral tissues is essential
    - When biologically active T3 is required, T4 can be converted into T3

    - When excessive T3 present, it can be inactivated locally to form rT3 (missing inner ring 5′)

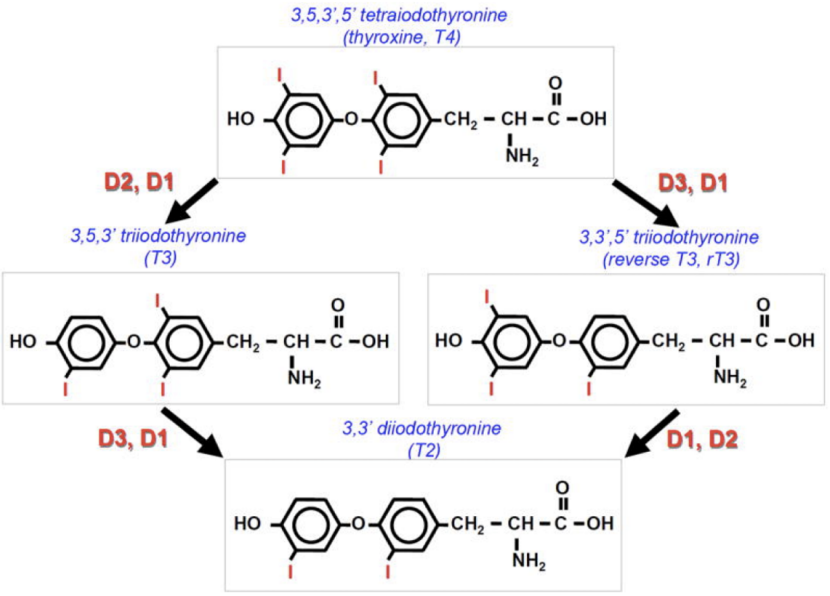
Thyroid hormone action

- Receptors for thyroid hormones are nuclear and bind T3
- The expression of nuclear receptors is very low
- Free thyroid hormone receptor (TR) without bound hormone, is bound to hormone response elements of DNA (HRE) and corepressor proteins (CoR)
- After T3 binds to its receptor, CoR is liberated and coactivators (CoA) is recruited and the transcription to mRNA begins

Tissue specificity

- Thyroid hormone levels vary remarkably between organs
    - E.g. T4 of the liver is 10x higher than that of skeletal muscle; T3 levels in the pituitary gland are significantly higher than in other tissue
- Factors that may contribute to these differences include
    - Relative amount of blood flow to tissues
    - Rates of T4 and T3 entry and release from cells
    - Amounts of intracellular binding sites
- Note the metabolism of thyroid hormones in cells is an important determinant of the amount of T3 that is available for binding to nuclear thyroid hormone receptors

Thyroid hormone metabolism



- Selenodeiodinases are a group of enzymes that play a crucial role in the metabolism of thyroid hormones.
- There are three main types of deiodinases in mammals, referred to as Type 1, Type 2, and Type 3 deiodinase (D1, D2, and D3, respectively).

Type 1 Deiodinase (D1)

- **Location and Function**: D1 is primarily located in the liver, kidneys, and thyroid gland. It can convert the **prohormone T4 into the active hormone T3** by removing an iodine atom from the outer ring (5′). D1 also contributes to the clearance of reverse T3 (rT3), an inactive metabolite of T4, by deiodinating it further.
- **Regulation and Impact**: D1's activity affects the overall circulating levels of T3 and T4, playing a significant role in maintaining systemic thyroid hormone balance.

Type 2 Deiodinase (D2)

- **Location and Function**: D2 is found in several tissues, including the brain, pituitary gland, brown adipose tissue, and skeletal muscle. It a**ctivates T4 to T3** by removing an iodine atom from the outer ring, similar to D1. However, D2's role is more localized, adjusting T3 levels within specific tissues to meet local metabolic demands.
- **Regulation and Impact**: D2 is pivotal for the brain's thyroid hormone supply, directly influencing neurodevelopment, thermogenesis in brown adipose

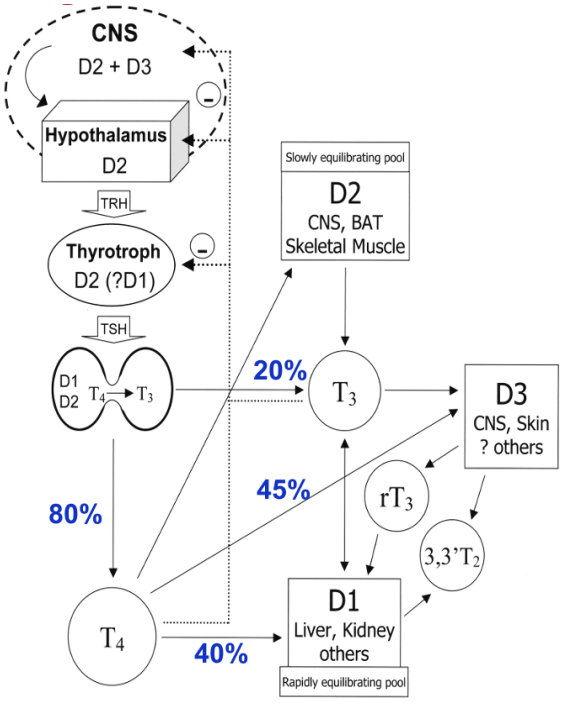
tissue, and overall energy metabolism. It's also involved in the feedback regulation of thyroid-stimulating hormone (TSH) in the pituitary.

Type 3 Deiodinase (D3)

- **Location and Function**: D3 is present in various tissues, including the CNS, placenta, skin, and developing organs. Unlike D1 and D2, D3 inactivates thyroid hormones by removing an iodine atom from the inner ring of T4 and T3, converting them into rT3 and 3,3'-diiodothyronine (T2), respectively, both of which are inactive.
- **Regulation and Impact**: D3 serves as a protective mechanism against excessive thyroid hormone action in specific tissues and is crucial during fetal development for regulating the local concentration of active thyroid hormones.

Summary

- The three deiodinases, D1, D2, and D3, together ensure that the right amount of thyroid hormone is available where and when it is needed, by either activating or inactivating these hormones.
- These enzymes' activities are finely tuned in response to the body's physiological demands, including development, metabolism, and response to environmental changes. Understanding the functions and regulation of D1, D2, and D3 is crucial for comprehending thyroid hormone physiology and its implications for health and disease.



The role of D1-3 in thyroid function

- T3, not T4, binds to the receptor.
- Outer ring (5′) deiodination can be viewed as the first step in the activation of the thyroid prohormone T4
- The tissue-specific regulation of T3 concentration, can occur in the absence of changes in T4
- The complexity of these interconnecting pathways illustrates the capacity for sophisticated local regulation of thyroid status, which is dependent on the existence of the selenodeiodinases

Importance of TH Transporters

- The intracellular nature of thyroid hormone metabolism requires transport of iodothyronines across the plasma membrane
- It was assumed for a long time that this occurs by passive diffusion, but it has become increasingly clear that cellular uptake and efflux of thyroid hormone is mediated by **transporter proteins**
- Recently, several specific thyroid hormone transporters have been identified, including monocarboxylate transporter 8 (MCT8), MCT10, and organic anion transporting polypeptide 1C1 (OATP1C1)
- OATP1C1 is expressed mainly in brain and transports mainly T4
- MCT8 appears to transport thyroid hormone in the brain, which is crucial during brain development
- It is expected that the study of thyroid hormone transporters will lead to a better understanding of the tissue-specific regulation of thyroid hormone bioavailability

Actions of thyroid hormones

- Increase basal metabolic rate
  - Increase the use of glucose and fatty acids for ATP production
  - Stimulate lipolysis
  - Increase body temperature (calorigenic effect)
- Promote balanced growth and CNS development
  - Regulate development and growth of nervous tissue and bones

Unique proteins

- Synthesis
  - Thyroid stimulating hormone receptor (TSHR) - follicular epithelial cells
  - Thyroid Peroxidase (TPO) - linking iodine to tyrosine
- Processing and release
  - TH transporters: MCT8, MCT10, OATP1C1
  - Proteolytic and lysosomal enzymes
- Tissue specific bioactivity
  - Selenodeiodinase (D1-3)

Steroid hormones

Hypothalamo-pituitary-adrenal axis

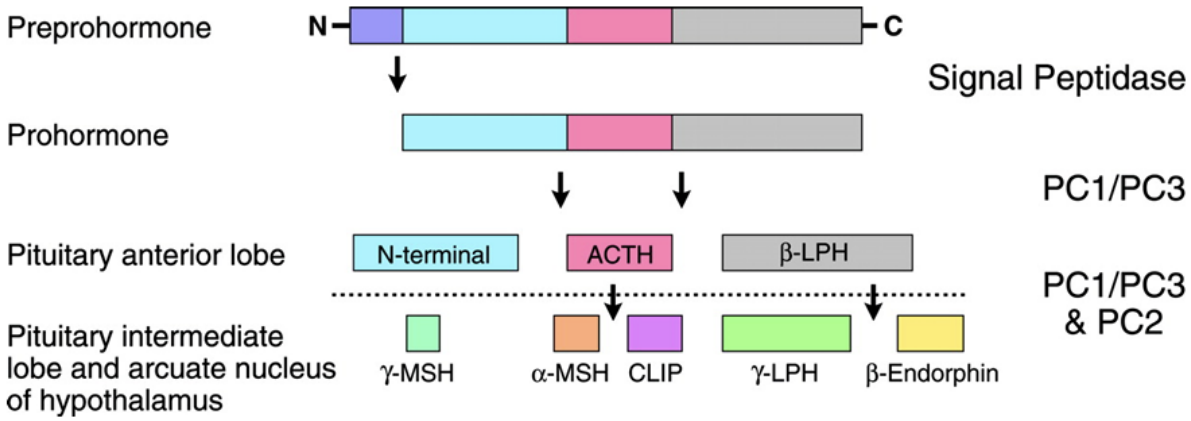
- Controlled by negative feedback
- Stress increases corticotropin releasing hormone (CRH)
- ACTH formed from cleavage of POMC

CRH from the hypothalamus stimulates release of corticotropin (ACTH) by the anterior pituitary. Corticotropin stimulates secretion of cortisol by adrenal cortex. Elevated cortisol inhibits release of corticotropin by anterior pituitary corticotrophs and CRH by hypothalamic neurosecretory cells.

- Long-term stress hormone: cortisol secreted by adrenal cortex
- Short-term stress hormone: adrenaline secreted by adrenal medulla

POMC processing

- Expression of Pro-POMC driven by CRH
- Signal peptidase cleave preprohormone (signal peptide) to generate POMC
- POMC is cleaved with **prohormone convertase (PC)** to generate pro-ACTH and beta-LPH
- Futher PC / endopeptidase action
  - ACTH
  - MSH (alpha-, beta-, gamma-)
  - Beta-endorphins

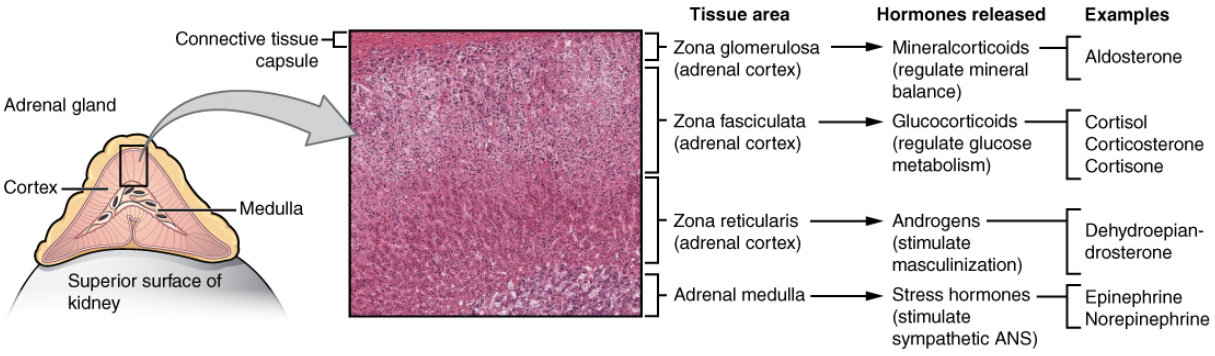


Mechanism of action

- Steroids are membrane-permeable and influence the nucleus of cells by direct action
- The steroid hormone penetrate the membrane of the target cell and binds to a receptor located in the cytoplasm of the cell (intracellular or intranuclear receptors)
- The hormone-receptor complex diffuses into the nucleus, where it either alters the expression of genes or activates additional cellular signals
  - Newly formed mRNA directs synthesis of specific proteins on ribosomes

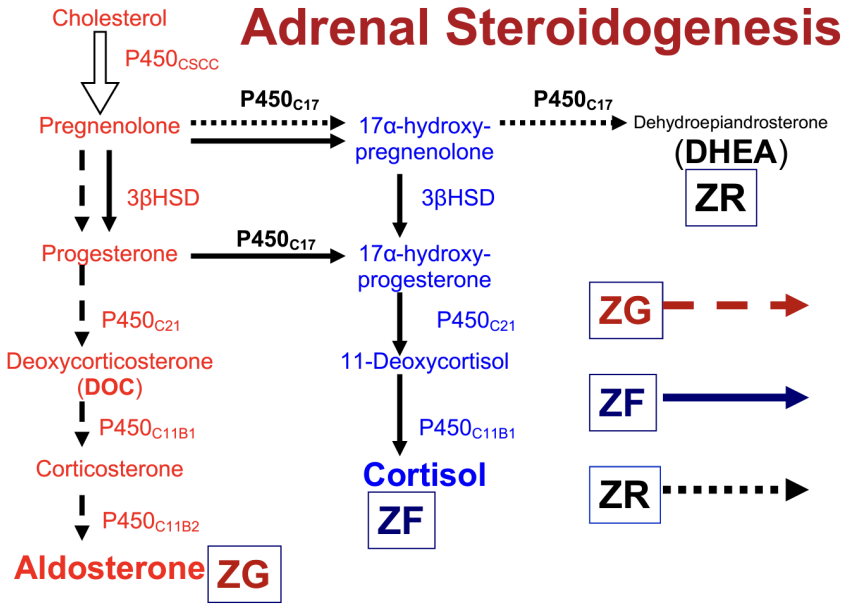
Biochemistry of steroidogenesis

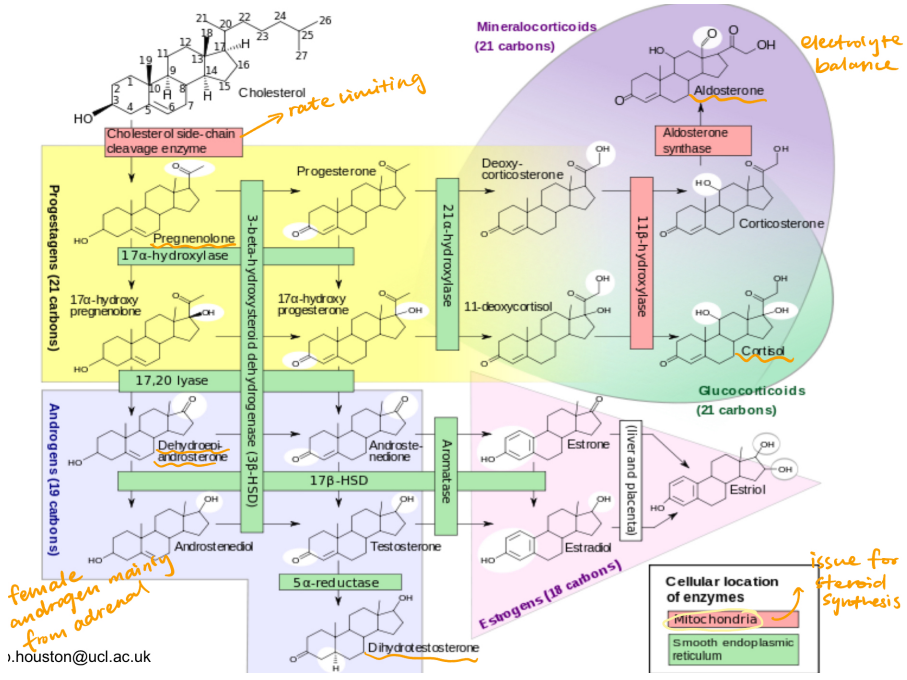
- **Rate determining step of ALL steroids is the conversion of cholesterol (C27) to pregnenolone (C21)**
  - Catalysed by P450cscc
  - Reaction catalysed in the mitochondria
- The sub-cellular location for P450cscc limit the rate of steroidogenesis because
  - P450cscc is on the inner mitochondrial membrane
  - Outer and inner mitochondrial memrbrane is separated by aqueous space
  - Thus requires transport protein - StAR (steroidogenic acute regulatory protein) - to shuttle cholesterol
- Zone-specific steroidogenesis



- Adrenal gland is organised into
  - Capsule
  - Zona glomerulosa - mineralocorticoids (C21)
  - Zona fasciculata - glucocorticoids (C21)
  - Zona reticularis - Androgen (C19)
  - Medulla
  - Central vein

Control of adrenal steroidogenesis





Congenital adrenal hyperplasia

P450C21 21-hydroxylase deficiency

- No conversion of progesterone to deoxycorticosterone and thus deficiency in aldosterone
  - This leads to salt-wasting (dehydration, low Na and high K)
- High level of androgen which causes masculinity and ambiguious genitalia in female infant

    - Excessive DHEA production due to increase in ACTH which is normally normally inhibited by negative feedback of cortisol to the hypothalamus
    - Less significant in male patient because the most androgen is produced by the gonad
- Elevated androgen levels can lead to early onset of puberty in both males and females.
- Adults with CAH may face fertility problems due to hormonal imbalances.

P450C11B1 deficiency

- 11β1-hydroxylase deficiency
- No conversion of deoxycorticosterone (DOC) to corticosterone and aldosterone; no conversion of 11-deoxycortisol to cortisol
- Salt sparing
    - DOC acts similarly to aldosterone and enough to preserve sodium, milder symptoms
    - Hypertension due to accumulation of mineralocorticoid precursors, DOC??
- DHEA in excess due to lack of feedback by cortisol to inhibit ACTH - masculinity in female

Corticosteroid receptors

	Type 1 Corticosteroid receptor	Type 2 corticosteroid receptor
Normal function	Mineralcorticoid receptor (MR)	Glucocorticoid receptor (GR)
In vivo natural ligands	Aldosterone (DOC)	Cortisol (Corticosterone)
Pharmacological ligands	Fludrocortisone	Detamethasone, Dexamethasone, Prednisolone etc.

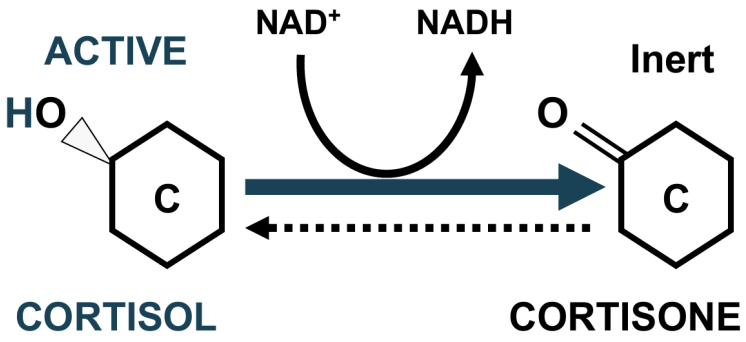
Dilemma of the MR

- MR has no inherent specificity for mineralocorticoids
    - Both cortisol and aldosterone may bind to MR

- [Cortisol]>100x [Aldosterone]
    - Cortisol = nmol/L; Aldosterone = pmol

How do MR's selectively respond to aldosterone?

- 11betaHSD oxidise glucocorticoids
    - Active cortisol is oxidised to inert cortisone



In human there are two HSD11beta isoforms:

- HSD11beta1
    - NADPH-dependent. Highly expressed in key metabolic tissues including liver, adipose tissue, and the CNS. In these tissues, HSD11beta1 reduces cortisone to the active hormone cortisol that activates GR.
- HSD11beta2
    - NAD independent. Expressed in aldosterone-selective tissues. In these tissues, HSD11beta2 oxidises cortisol to cortisone and prevents illicit activation of the MR.

Apparent mineralocorticoid excess

Why might 11betaHSD fail?

- Type 1 AME: mutations in 11betaHSD2 gene
    - Coding sequence (loss of function)
    - Regulatory region (decreased expression)
- Type 2 AME: enzyme inhibition
    - Glycyrrhizic acid, gossypol, bioflavinoids

If 11betaHSD is fully active, why might cortisol gain inappropriate access to MR?

- Sustained high [Cortisol]
  - e.g. Cushing's disease, glucocorticoid resistance
  - GR not funcitoning, and the body produce excessive corticol in compensation
  - Note that corticol due to stress is usually not sustained
- Exceed capacity of enzyme to inactivate cortisol

Placenta 11betaHSD protects fetus

- 11betaHSD protects fetus from cortisol in maternal circulation by inactivating them to cortisone
- Cortisol causes premature differentiation of cell instead of proliferation

Consequences of failure of placental 11betaHSD

- Increased passage of cortisol to fetus
- Stimulates premature differentiation of fetal tissues
- Prevents further growth of tissues
- Culminates in IUGR (Intrauterine Growth Retardation)
- Barker hypothesis - increased risk of serious adult disease (preprogrammed stress response)

	Type 1 11betaHSD	Type 2 11betaHSD
Sites of expression	Ubiquitous; highly expressed in metabolic tissues such as liver, adipose tissue, CNS	Kidney, colon, parotid gland, placenta (where aldosterone acts)
Cofactor	NADPH	NAD+
Major direction of action	Reductase	Dehydrogenase
Function	Generates active glucocorticoid	Renders glucocorticoid inactive