

# Introduction to Endocrinology

Endo 1 - Professor John Laycock & Dr. Chris Long ([j.laycock@imperial.ac.uk](mailto:j.laycock@imperial.ac.uk) & [c.long@imperial.ac.uk](mailto:c.long@imperial.ac.uk))

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1. Define the terms hormone, endocrine gland, neurotransmitter and neurosecretion.
2. Identify the features which distinguish endocrine from paracrine and autocrine systems.
3. State that most hormones can be classified either as protein (and polypeptide) or steroid hormones, but that a few do not fall easily into either of these two groups and therefore form a third group.
4. Describe the principal stages of protein/polypeptide hormone synthesis, how they are stored and the mechanism of their secretion into the circulation.
5. Describe the different types of membrane receptor and the intracellular mechanisms of action induced by hormones.
6. Explain how steroid hormones are synthesised and released into the circulation.
7. Describe the receptors and mechanisms of action of steroid hormones.
8. Define the terms negative and positive feedback and explain how any individual hormone system is controlled.

## Definitions

**ENDOCRINE GLAND:** a group of cells which secrete "messenger" molecules directly into the bloodstream

**ENDOCRINOLOGY:** study of endocrine glands and their secretions

**HORMONE:** the bioactive "messenger" molecule secreted by an endocrine gland into the blood, i.e. not simply a metabolite or energy substrate

**ENDOCRINE:** relates to hormone's action on target cells at a distance from source

**PARACRINE:** relates to hormone's action on nearby target cells e.g. within immediate area around source

**AUTOCRINE:** relates to hormone having an effect on its own immediate source

**CRYPTOCRINE:** a term devised to indicate that a hormone can have an effect within its own cell of production, i.e. hidden

Endocrine System	Nervous System
Release of chemical (HORMONE) into bloodstream	Release of chemical (NEUROTRANSMITTER) across synapse
Effect can be on many target cells spread throughout the body	Effect will be restricted to those target cells actually innervated
Effect will take place over a relatively long time-span ranging from seconds to days	Effect will be generated within milliseconds

## Endocrine Glands

### *Classic*

- Gonads
- Pancreas
- Adrenals
- Thyroid
- Parathyroids
- Pituitary

### *More Recently Identified*

- Kidneys
- Heart/blood
- Liver

- Brain
- Fat (adipose) tissue
- Placenta

### Hormone Classification

- There are three classifying classes of hormones:
  - Protein/polypeptide hormones
  - Steroid hormones
  - miscellaneous

### Hormone synthesis, storage and release from endocrine tissues

#### *Protein/polypeptide hormones*

- **E.g. Adrenocorticotrophic hormone (ACTH)**
- Precursor is known as a PRO-HORMONE, and in this case is pro-opiomelanocortin (POMC); an 241 amino acid long chain with Ser at the amino terminus, and Phe at the carboxyl terminus
- POMC is produced in the ANTERIOR PITUITARY GLAND (just below the hypothalamus, but lies outside the blood-brain barrier)
- Blood perfuses the anterior pituitary gland, delivering and removing substrates
- Amino acids are provided by the diet and via the blood enter the cytoplasm of a CORITCOTROPH CELL (ACTH secretory cells) within the anterior pituitary gland—stimulates the transcription and translation of precursor POMC in the endoplasmic reticulum.
- Vesicles containing POMC are transported into the golgi, where they undergo post-translational modification and processing by enzymes to form ACTH.
- ACTH is then stored in vesicles within the cell, waiting for a STRESS SIGNAL for exocytosis (secretion of the hormone)

#### *Steroid Hormones*

- **E.g. Cortisol**
- Major stress hormone
- Precursor molecule is STEROID, which is transported via low density lipoproteins LDL as FATTY ACID ESTERS to ADRENAL CORTICAL CELLS within the ADRENAL GLANDS
- Stress stimulus → breakdown of fatty acid esters using enzymes e.g. ESTERASE, liberating the cholesterol
- Cholesterol then needs to be transported into the MITOCHONDRIA of the adrenal cortical cell. The inner and outer membrane of mitochondria is AQUEOUS, therefore StAR PROTEIN is required to act as a transporter of the cholesterol into the mitochondria. This can be seen as RATE LIMITING.
- Once in the mitochondria, cholesterol is converted to the steroid hormone of choice, in this case CORTISOL
- As soon as the steroid hormone of choice is produced, it diffuses across the PLASMA MEMBRANE of the adrenal cortical cell into the blood circulation
- Steroid hormones bind to a large number of PLASMA PROTEINS within the blood, which prevent the hormone from being degraded.
  - LOW AFFINITY HIGH CAPACITY proteins = ALBUMIN
  - HIGH AFFINITY LOW CAPACITY proteins = BINDING GLOBULINS, in this case Cortisol binding globulins; GBG
- Only free steroid hormones are biologically active, therefore they cannot have an effect on their target tissue if bound to a plasma protein

### Hormone transport within the blood

- When steroid hormones bind with plasma proteins in the blood, they form a PLASMA PROTEIN BOUND HORMONE. This formation reaches EQUILIBRIUM
- If the FREE HORMONE is used up by the TARGET TISSUE, its concentration will decrease therefore the position of equilibrium will shift to oppose this change, i.e. the ENDOCRINE GLAND will increase hormone synthesis and release from the plasma protein
- Conversely, if the concentration of plasma protein bound hormone INCREASES (which occurs during pregnancy), the position of equilibrium will shift to oppose the change to try to form more of the protein-hormone complex. This will result in a DECREASE in the PLASMA PROTEIN concentration in the blood.

### Hormone mechanism of action at target tissues

#### *Protein/polypeptide hormones*

- E.g. ACTH
- ACTH is transported to the ADRENAL CORTICAL CELLS in the ADRENAL GLANDS via the blood, where it binds to the ACTH G-PROTEIN LINKED RECEPTOR
- Binding → dissociation of the G-PROTEIN which activates ADENYLATE CYCLASE
- Adenylate cyclase then increases the conversion of ATP → c-AMP (CYCLIC AMP)
- c-AMP activates PROTEIN KINASE A, which stimulates INCREASED cholesterol release from fatty acid esters, and increased uptake into mitochondria via StAR protein → increased CORTISOL SYNTHESIS

#### *Steroid Hormones*

- Only free steroid hormones are able to freely diffuse across the plasma membrane of their target cell, where they bind to an INTRACELLULAR RECEPTOR
- The complex is then TRANSLOCATED into the nucleus, where it MODIFIES PROTEIN TRANSCRIPTION of a new protein

### Hormone feedback

- NEGATIVE FEEDBACK cycle
- **Stress** stimulus **stimulates** the synthesis and release of **ACTH** from the anterior pituitary gland, which is transported via the blood to the adrenal gland
- **ACTH** in the adrenal gland **stimulates** the synthesis and release of **Cortisol** into the bloodstream
- When **cortisol** reaches the anterior pituitary gland, this **inhibits** the synthesis of **ACTH**

# The Hypothalamo-adenohypophysial axis

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1. Draw a labelled diagram showing how hypothalamic hormones reach their target cells in the adenohypophysis (anterior pituitary) using the terms hypothalamic nuclei, neurosecretions and hypothalamo-hypophysial portal system.
2. Identify the six chief adenohypophysial hormones and relate them to the hypothalamic hormones which control them, indicating whether the latter hormones stimulate or inhibit their production.
3. Describe the general features of synthesis, storage and release of the adenohypophysial hormones, including the pre-prohormone and prohormone stages when relevant.
4. Describe the principal physiological actions of corticotrophin (ACTH), thyrotrophin (TSH) and the two gonadotrophins (LH and FSH).
5. Draw a diagram illustrating direct, indirect and short negative feedback loops, using the hypothalamo-adenohypophysial-thyroidal axis for your example.
6. Describe the growth promoting and metabolic actions of somatotrophin (growth hormone).
7. Draw a labelled diagram illustrating the various controlling influences on somatotrophin release.
8. List the various actions of prolactin indicating which one is its principal physiological effect.
9. Draw a labelled diagram illustrating how prolactin release is controlled, using the term neuroendocrine reflex arc.

## Overview

- The PITUITARY GLAND (also known as the HYPOPHYSIS) lies at the base of the brain in the SELLA TURCICA directly under the HYPOTHALAMUS
- **The hypothalamus:**
  - Regulates the endocrine system
  - Lies around the 3<sup>RD</sup> VENTRICLE in the brain
  - Anterior: OPTIC CHIASMA lies at the front of the hypothalamus, and has an important role in sight
  - Posterior: MAMMILLARY BODY at the back of the hypothalamus is important in the development of the nervous system
- **Development of the pituitary gland:**
  - ANTERIOR LOBE (ADENOHYPOPHYSIS) - “grows up” and attaches to the base of the brain.
  - POSTERIOR LOBE (NEUROHYPOPHYSIS) – nervous tissue “grows down” and attaches to the anterior lobe; consists mainly of nerve axons and nerve terminals

## *Link between the Hypothalamus and the Pituitary Gland*

- The region between the Hypothalamus and the pituitary gland is known as the REGION OF MEDIAN EMINENCE
- Within the hypothalamus, HYPOTHALAMIC NUCLEI are present. These are clusters of nerve cell bodies. There are two types of neurones within these clusters:
  - Neurones that pass through the region of median eminence and end at the NEUROHYPOPHYSIS within the pituitary gland
  - Neurones that terminate at the region of median eminence

## *The Hypothalamo-hypophysial portal system (i.e. circulation)*

- Blood supply to the Region of Median Eminence is by the SUPERIOR HYPOPHYSIAL ARTERY
- When a hypothalamic neurone is activated, HYPOTHALAMIC NEUROSECRETION occurs

- NEUROSECRETIONS (hypothalamic releasing/inhibiting hormones) are released within the HYPOTHALAMO-HYPOPHYSIAL PORTAL SYSTEM
- Capillary collection of the neurosecretions in the Region of Median Eminence is by the fenestrated PRIMARY CAPILLARY PLEXUS
- Circulation of the neurosecretions is within the LONG PORTAL VEINS and the SECONDARY CAPILLARY PLEXUS
- The hypothalamic neurosecretion acts on the ANTERIOR PITUITARY TARGET CELLS, which release ADENOHYPOPHYSIAL HORMONE into the CAVERNOUS SINUS, and then into the general circulation via the JUGULAR VEINS

### Adenohypophysial Cells

<i>Cell</i>	<i>Hormone Produced</i>
<b>Somatotrophes</b>	<b>Somatotrophin</b> (growth hormone)
<b>Lactotrophes</b>	<b>Prolactin</b>
<b>Thyrotrophes)</b>	<b>Thyrotrophin</b> (thyroid stimulating hormone; TSH)
<b>Gonadotrophes</b>	<b>Gonadotrophins</b> (Leutinizing hormone; LH Follicle stimulating hormone; FSH)
<b>Corticotrophes</b>	<b>Corticotrophin</b> (adrenocorticotrophic hormone; ACTH)

There are many other cells of undefined function

NB: cells can also produce/release other molecules that may have paracrine, autocrine or endocrine effects

### Adenohypophysial Hormones

- Precursor molecules are called PROHORMONES
- ENZYMATIC CLEAVAGE of prohormone → bioactive HORMONE molecule
- ADENOHYPOPHYSIAL HORMONES stored in secretory granules, and are released by exocytosis
- All consist of amino acids, but can be divided into three categories

#### 1. Proteins

- **SOMATOTROPHIN**
  - Growth hormone
  - 191 amino acids
- **PROLACTIN**
  - 199 amino acids

#### 2. Glycoproteins

- Consist of an alpha and beta sub-unit
- Alpha sub-unit common to all – 92 amino acids
- Specificity of hormone lies in the number of amino acids in the beta sub-unit
- **THYROTROPHIN**
  - 110 amino acid beta sub-unit
- **GONADOTROPHINS**
  - LH and FSH

- Both have a 115 amino acid beta sub-unit

### 3. Polypeptides

#### ➤ CORTICOTROPHIN

- ACTH
- 39 amino acids

### *Release of Adenohypophysial hormones*

HYPOTHALAMIC HORMONES have a direct influence on the release of adenohypophysial hormones:

- **Somatotrophin**
  - SOMATOTROPHIN RELEASING HORMONE (SRH/GHRH) → stimulates release
  - SOMATOSTATIN (SS) → inhibits release
- **Prolactin**
  - DOPAMINE (DA) → inhibits release (is also dominant hormone controlling prolactin release)
  - THYROTROPHIN RELEASING HORMONE (TRH) → stimulates release
- **Thyrotrophin**
  - THYROTROPHIN RELEASING HORMONE (TRH) → stimulates release
- **Gonadotrophins (LH & FSH)**
  - GONADOTROPHIN RELEASING HORMONE (GnRH) → stimulates release
- **Corticotrophin (ACTH)**
  - CORTICOTROPHIN RELEASING HORMONE (CRH) → stimulates release
  - VASOPRESSIN (VP) → stimulates release (secondary)

### *Main Target Cells*

- Somatotrophin → general body tissue, especially the liver
- Prolactin → breasts (lactating women)
- Thyrotrophin → thyroid
- Gonadotrophins → testes (men), ovaries (women)
- Corticotrophin → adrenal cortex

### Somatotrophin

- Secreted from the adenohypophysis (anterior pituitary lobe) and is transported to the body tissues and Liver
- Binding to receptors on general body tissues → metabolic actions → growth and development
- Binding to receptors on liver → release of SOMATOMEDINS; mediators- IGF I and IGF II
- Somatomedin metabolic actions:
  - Stimulation of **amino acid transport** into cells e.g. muscles
  - Stimulation of **protein synthesis**
  - Increased **cartilage growth**
  - Stimulation of **lipid metabolism** leading to increased fatty acid production
  - Increased **insulin resistance**, leading to decreased glucose utilization and increased blood glucose concentration

*Control of somatotrophin production***Negative Feedback**

- Somatotrophin and somatomedin release in itself inhibits further somatotrophin production via negative feedback loops
- SOMATOSTATIN (SS) → inhibits release

**Positive feedback**

SOMATOTROPHIN RELEASING HORMONE (SRH/GHRH) → stimulates release

Other things that stimulate somatotrophin production include:

- Sleep stages III and IV
- Stress
- Oestrogens
- Exercise
- Fasting/hypoglycaemia
- Amino acids
- GHRELIN (from stomach)

Prolactin*Effects*

- Main physiological effect:
  - **BREAST LACTOGENESIS in post-partum women**
- Other effects:
  - Increased number of LH receptors in Gonads
  - Renal Na<sup>+</sup>/Water reabsorption
  - Steroidogenesis
  - Immunological effects, e.g. stimulates T cells
- Effects during high circulating levels:
  - Decreased LH release from the pituitary gland
  - Decreased sexual behaviour – involves hypothalamus

*Control of prolactin production*

- Stimulus: suckling- stimulation of tactile receptors on breast nipple
- Inhibition of DA and stimulation of TRH via AFFERENT NEURAL PATHWAY
- OESTROGENS and IODOTHYRONINES also stimulate prolactin
- Prolactin stimulates milk production via the ENDOCRINE EFFERENT NEURAL PATHWAY
- This is known as a NEUROENDOCRINE REFLEX ARC

# Tutorial 1: Adenohypophysial Disorders

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## Case History

A **10-year-old boy** was seen by his GP because the parents were concerned about his lack of growth which they had become increasingly aware of because his younger brother (aged 6.5 years) was already taller by 2 cm. His height and body weight were recorded as **120 cm** and **25 kg** respectively, giving a **BMI of 17.4 kg/m<sup>2</sup>**. The boy's **proportions were perfectly normal**, and apart from the short stature **no other abnormalities** were seen on examination. From the family history there was clearly **no evidence of malnutrition** or emotional deprivation, and the **mid-parental height** gave an expected height of **166 cm**. The boy's recorded **height 2 years previously** (according to the practice records) was **116 cm**.

Standard growth curves are shown on the next page

## Questions:

### 1. Examine standard growth charts for boys and girls and interpret the various lines shown.

- Growth lines indicate percentiles: there is usually a large variation in height
- The patient is in the lowest 3<sup>rd</sup> percentile of the population
- The patient does not have a genetic defect due to the following reasons:
  - 2 years ago he was above the 3<sup>rd</sup> percentile
  - His expected height (based on mid-parental height) is greater than his current height
  - His younger brother is taller than him
  - His proportions are normal; therefore he does not have dwarfism
- Use of growth charts:
  - It is important to take multiple height measurements over a period of time in order to establish a basis for comparison
  - A single height measurement is *not* sufficient
  - The growth chart must be specific to the population to which an individual belongs

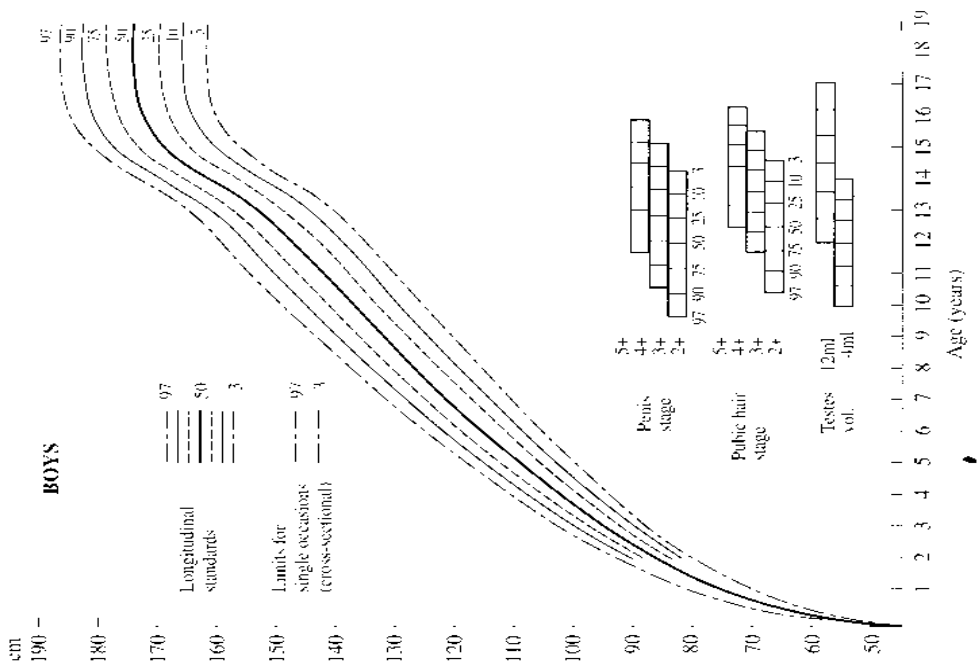
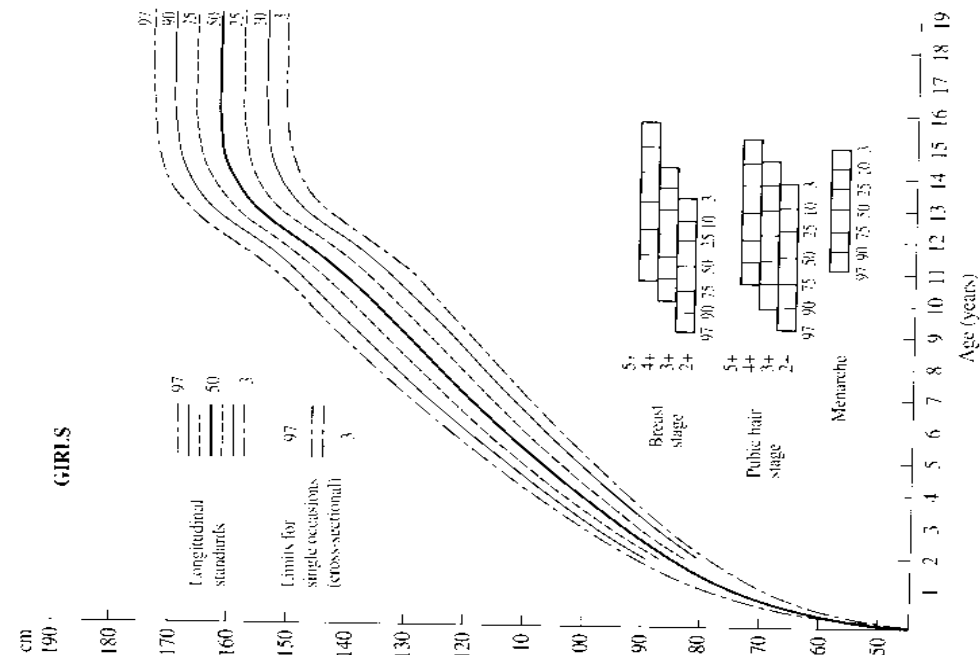
### 2. What are the various causes of short stature?

- Malnutrition
- Genetic causes: e.g. Down syndrome; osteochondroplasia (genetic dwarfism); Turner's syndrome; Prader-Willi syndrome
- Low levels of somatotrophin (GH)
- Low levels of SRH/GHRH
- High levels of somatostatin (SS)
- High levels of somatomedins (IGF1 and IGF2)
- Somatotrophin resistance due to a lack of receptors or dysfunctional receptors
- Hypothyroidism
- Cushing syndrome: excess glucocorticosteroids

### 3. How would you design a GH stimulation test?

- Purpose of a GH stimulation test: to identify whether or not the GH axis is functioning correctly
- GH is released in pulses at different times throughout the day and with varying magnitudes
- GH release must be stimulated (by exercise/stressors/fasting/insulin injection)
- Its level must be measured at different times throughout the day





# The hypothalamo-neurohypophysial system

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1. Draw a simple labelled diagram identifying the principal features of the neurohypophysial system.
2. Name the two neurohypophysial hormones and indicate how their chemical structures differ.
3. Describe the principal steps involved in the synthesis, storage and release of the neurohypophysial hormones.
4. Name the receptors for vasopressin and the major intracellular pathway activated through each receptor.
5. Name target cells for each of the vasopressin receptors.
6. List the principal physiological actions of the neurohypophysial hormones.
7. Relate the actions of the hormones to their receptor types.
8. Draw a labelled diagram illustrating the principal physiological action of vasopressin on renal water reabsorption.
9. Describe the control systems involved in the production of the neurohypophysial hormones
10. Draw a simple diagram illustrating the neuroendocrine reflex arc for oxytocin.

## Overview

- Two HYPOTHALAMIC NUCLEI (collection of cell bodies) are associated with the POSTERIOR PITUITARY GLAND:
  - PARAVENTRICULAR nucleus; axons pass through median eminence and terminate in the NEUROHYPOPHYSIS
  - SUPRAOPTIC nucleus; axons pass through the median eminence and terminate just above the OPTIC CHIASMA in the neurohypophysis
- There are effectively two types of neurones within the paraventricular nucleus:
  - MAGNOCELLULAR neurones are larger (and are the majority), and pass through the median eminence and terminate on the neurohypophysis
  - PARVOCELLULAR neurones are smaller, and either terminate on the PRIMARY CAPILLARY PLEXUS at the median eminence, or in other parts of the CNS (acting as neurotransmitters)
- Supraoptic neurones are also magnocellular.
- Magnocellular Neurones:
  - Larger than parvocellular
  - Terminate in the neurohypophysis, i.e. pass through the median eminence
  - Have “swellings” along their axons, known as HERRING BODIES
  - Herring bodies are granules that accumulate the newly synthesised hormones within the axon/dendrites, forming swellings which then release the hormones into the general circulation
- Both paraventricular and supraoptic neurones are either VASOPRESSINERGIC or OXYTOCINERGIC
  - Vasopressinergic neurones secrete VASOPRESSIN
  - Oxytocinergic neurones secrete OXYTOCIN
- Other hypothalamic neurones, e.g. in the SUPRACHIASMATIC nucleus (effectively the biological clock) produce vasopressin

## Synthesis

### *Vasopressin*

- Precursor molecule (pre-prohormone) is PRE-PROVASOPRESSIN
- This is synthesised and then processed in granules (like the herring bodies) to form PRO-VASOPRESSIN (pro-hormone)
- Pro-vasopressin is then further processed to form:
  - VASOPRESSIN (AVP- arginine vasopressin)
  - NEUROPHYSIN proteins (NP- role unknown)
  - GLYCOPEPTIDE (GP- role is being researched currently)
- These products are formed in EQUIMOLAR amounts
- Released as NEUROSECRETIONS of hormone and neurophysin proteins

### *Oxytocin*

Oxytocin synthesis has the same sequence of events as vasopressin synthesis, although the neurophysin differs slightly, and the glycopeptide is absent.

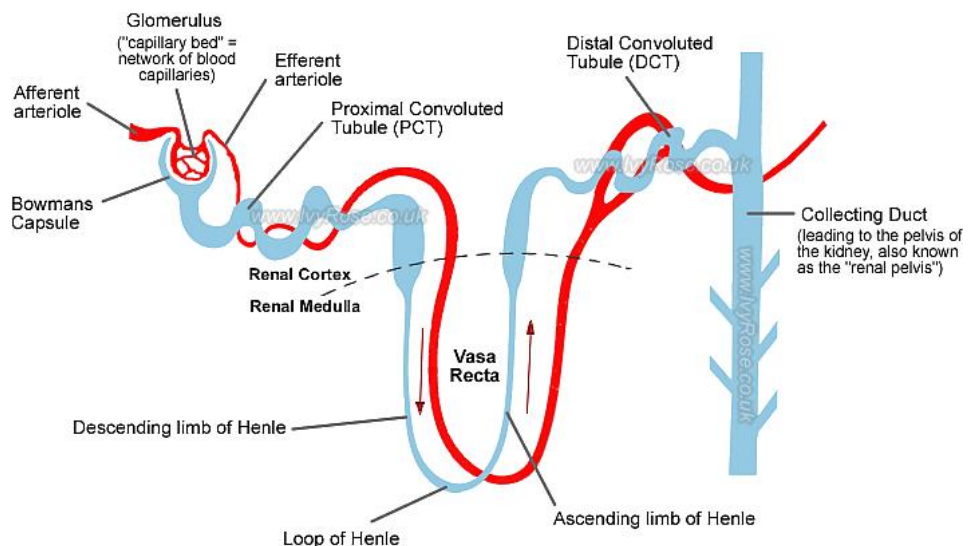
## Structure

- Both vasopressin and oxytocin exhibit a RING structure with 6 AMINO ACIDS
- They also have a small attached CHAIN or PRE-AMINO ACIDS
- Differ by 2 amino acids
- Difference within the **ring** structure; Vasopressin has **Phe replaced by Ile** in Oxytocin
- Difference within the **chain** structure; Vasopressin has **Arg replaced by Leu** in Oxytocin

## Vasopressin

### *Actions*

- Principal physiological action:
  - water reabsorption in the PRINCIPAL CELLS (receptors) within the RENAL COLLECTING DUCTS
  - controls final concentration of urine
  - ANTIDIURETIC effect
- Other actions:
  - **Vasoconstriction** -- of smooth muscle in the vascular system, particularly arterioles
  - **Corticotrophin (ACTH) release (together with CRH)** -- by PARVOCELLULAR neurones
  - **CNS effects** -- neurotransmitters affect behaviour- receptors in HYPOCAMPUS



- In order to have an effect, presence of RECEPTOR is required to mediate the effect of the neurotransmitter
- There are many locations of vasopressin receptors away from the vasopressinergic neurones; vasopressin is perhaps carried in the CSF (CEREBROSPINAL FLUID)
- **Synthesis of blood clotting factors (VIII and Von Willbrandt factor)**
- **Hepatic Glycogenolysis**- STRESSORS increase blood glucose concentration, therefore can be said that stressors lead to VP secretion

### Receptors

#### ➤ **V1 receptors:**

- G-protein linked receptor which activate PHOSPHOLIPASE C (enzyme)
- Phospholipase C acts on membrane phospholipids to produce INOSITOL TRIPHOSPHATE; IP<sub>3</sub> (and DIACYL GLYCEROL; DAG)
- IP<sub>3</sub> and DAG increase free cytoplasmic Ca<sup>2+</sup> and other intracellular mediators (PKC) → cellular response
  - **V1a receptor locations:**
    - Vascular smooth muscle → Vasoconstriction
    - Hepatocyte → Glycogenolysis
    - CNS parvocellular neurones → behavioural effects
  - **V1b (Also known as V3) receptor location:**
    - Adenohypophysial corticotrophs → ACTH production

#### ➤ **V2 receptors:**

- G-protein linked receptor which activate ADENYL CYCLASE (enzyme)
- Adenyl cyclase catalyses the conversion of ATP → c-AMP
- C-AMP acts as a SECOND MESSENGER MOLECULE to activate PROTEIN KINASE A (PKA)
- Protein kinase A activates other intracellular mediators → cellular response
- Cellular response: synthesis of AQUAPORINS, especially AQP2.
- AQP2 is a water protein-channel which is needed for water reabsorption in the kidney collecting duct, which is VAOPRESSIN DEPENDENT and present in the APICAL MEMBRANE of principal cells
  - **Receptor location:**
    - Collecting duct cells → water reabsorption
    - Other unidentified sites (e.g. endothelial cells → vasodilator effects)
    - Blood clotting factors (VIII and Von Willbrandt factors)

### Kidney Collecting Duct Cell

- V2 receptor lies on BASOLATERAL membrane (G-protein linked receptor with adenylate cyclase)
- Osmotic gradient across cell increases from tubule lumen to the plasma
- Synthesis of APQ2 → migration of AGGRAPHORES to APICAL membrane (facing lumen) and insertion of APQ2 into membrane
- AQP2 then acts as protein channel for water absorption from the tubule lumen into the cell
- AQP3 and AQP4 lie in the BASOLATERAL MEMBRANE, and act as protein channel for water transport out of the cell

### *Vasopressin Control*

First consider two **roles of vasopressin**:

1. Water Reabsorption
2. Vasoconstriction

➤ **Water Reabsorption**

- Stimulus: increased plasma osmolarity (esp. Increase in Na<sup>+</sup> conc), therefore water leaves collecting duct cell
- OSMORECEPTORS in the brain respond to this increase:
  - Increase activation of neurones
  - Increase vasopressin secretion into general circulation
  - Increased water reabsorption into nephron
- Response: decreased plasma osmolarity

➤ **Vasoconstriction**

- Stimulus: decreased arterial blood pressure
- BARORECEPTORS in CAROTID SINUS and AORTIC ARCH **decrease frequency of stimulus**
  - **Decreased** stimulus on SYMPATHETIC nervous system
  - Increased vasopressin secretion
  - Increased vasoconstriction
- Response: increased arterial blood pressure

NB: there are also influences from higher centres, e.g. stress. For example anaesthetics + surgery = stress → increased vasopressin release

### Oxytocin

#### *Actions*

➤ **UTERUS at PARTURITION**

- ➔ MYOMETRIAL cells contract
- ➔ Delivery of baby

➤ **BREAST during LACTATION**

- ➔ MYOEPIHELIAL cells contract
- ➔ Milk ejection

Note: PROLACTIN stimulates the **synthesis** of breast milk, OXYTOCIN stimulates is **ejection**

#### *Neuroendocrine Reflex arc*

- Stimulus: suckling
- Receptors: around nipple
  - Activation of the NEURAL AFFERENT LIMB
  - Increased oxytocin release from the neurohypophysis
  - Activation of the ENDOCRINE EFFERENT LIMB
- Response: Milk ejection

Note: the same arc occurs from prolactin, except for milk synthesis

### Clinical Effects

- Oxytocin: milk can be artificial, and delivery can be induced therefore not very important
- Vasopressin: a decrease in vasopressin may lead to DIABETES INSIPIDUS, or SIADH (syndrome of inappropriate ADH)

### *Diabetes insipidus*

- Lose too much water therefore excess urine
- CENTRAL diabetes insipidus is caused by NO VASOPRESSIN
- NEPHROGENIC diabetes insipidus is caused by TISSUE INSENSITIVITY
- Net result is the same: DIURESIS, POLYURIA and POLYDIPSIA
- Polyuria: excessive urine
- Polydipsia: excessive drinking

## Tutorial 2: Neurohypophysial Disorders

Endo 3 - Professor K Meeran ([k.meeran@imperial.ac.uk](mailto:k.meeran@imperial.ac.uk))

### Case History

A **27-year old woman** attended her GP's surgery complaining of a continuous unquenchable **thirst**. She felt a constant need to drink water and consumed around 20 large glasses every day. She also kept water beside her bed since she was **woken every night** by her thirst. She also needed to **urinate very frequently**. On referral to an endocrine clinic it was found that her **fasting serum glucose** level was normal and **no glucose was detected in her urine**. She was then given a **water deprivation test** in which she was not allowed to drink but was asked to provide urine samples every hour. After the 11.00 am sample had been taken she was given a dose of a **modified form of vasopressin** (DDAVP) as a nasal spray. The **osmolality of her urine** samples were measured (a high osmolality representing concentrated urine).

	Patient's response		Typical normal person's response	
Time	Urine osmolality	Urine volume	Urine osmolality	Urine volume
9.00	130	175	620	95
10.00	158	180	850	70
11.00	204	140	1090	50
11.01	DDAVP administered			
12.00	886	70	1180	40

### Questions

1. **What would you expect to happen to the osmolality of urine during water deprivation test?**
  - Urine osmolality would increase since high blood glucose level exerts an osmotic pressure which draws water out of the plasma and into the renal filtrate
  - This leads to:
    - Polyuria: increased urine volume
    - Polydipsia: excessive thirst

2. **Why did the osmolarity of her urine rise after the administration of DDAVP?**
  - DDAVP stimulates water reabsorption in the principal cells of the renal collecting ducts
  - Increased water reabsorption in the renal collecting ducts causes the osmolality of her urine to rise
3. **What could be the underlying cause of her condition?**
  - She is sensitive to vasopressin since DDAVP has the desired physiological effects
  - Therefore the cause of her disease is a lack of vasopressin due to any of the following:
    - Genetic disorder
    - Cranial diabetes insipidus: this results in the production of dilute urine (as opposed to diabetes mellitus)
    - Hypothalamic disorder which affects vasopressinergic neurones: e.g. due to trauma or a tumour
    - Hypophysial disorder: e.g. due to inflammation
4. **What further measurements could be made?**
  - Vasopressin may be measured following stimulation of vasopressin release using hypotonic saline

## Insulin Secretion & Intermediary Metabolism

Endo 4 - Dr Stephen Robinson ([Stephen.robinson@imperial.ac.uk](mailto:Stephen.robinson@imperial.ac.uk))

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1. Explain why the blood glucose concentration is closely regulated and list the hormones that control it.
2. Draw a labelled diagram illustrating the relationship between the different types of cell in the islets of Langerhans. Describe the endocrine pancreas.
3. Give an overview of the principal metabolic pathways for carbohydrates, proteins and fats, and the hormones that regulate these pathways.
4. Describe the structure of a typical islet of Langerhans, identifying the different cellular components and their principal endocrine secretions.
5. Describe the main features of insulin synthesis, storage and secretion.
6. List and describe the principal actions of insulin
7. Discuss the insulin receptor and its function.
8. Draw a labelled diagram illustrating the factors which regulate the release of insulin.
9. Describe the synthesis, storage and secretion of glucagon.
10. List and describe the principal actions of glucagon.
11. Draw a labelled diagram illustrating the factors which regulate the release of glucagon.
12. Describe in your own words what the diagnosis of diabetes means to patients (video)
13. Describe the beta-cell sensing mechanism of glucose
14. Describe the endocrine regulation of intermediary metabolism

### Diabetes Mellitus

- Blood glucose concentration elevation and lack of controlled physiological feedback loop
- **Type 1 Diabetes Mellitus** (T1DM): elevated blood glucose concentration where insulin is required to prevent KETOACIDOSIS
- **Type 2 Diabetes Mellitus** (T2DM): more common, considerable health problem; defined in terms of glucose but also related to HYPERTENSION and DYSLIPIDAEMIA
- T1DM is the cause of approx 11% of UK diabetes, and T2DM approx 85-95%
- **Treatment** (to help symptoms, complications; morbidity and mortality):
  - Diet- important, but less important due to new developments in treatment

- Insulin- correct amount of insulin is vital (this is an important role of the pancreas)
- Glucose monitoring:
  - Capillary glucose monitoring monitors due to the lack of physiological feedback loop into the pancreas
  - Average blood glucose can be measured using Hb concentration as glucose binds to Hb
- Hypoglycaemia occurs when there is an imbalance between diet, exercise and insulin
- Maturity Onset Diabetes of the Young (MODY) – single gene defect → diabetes. Behaves like T2DM, but occurs in younger people (15-30 yrs olds) and is not a polygenic disease. However is used to help understand the mechanisms that bring about T2DM
- MODY only accounts for 3% of UK diabetes cases
- Over years, diabetes results in an increase in complications, reduction in life expectancy etc

### Glucose

- Very important energy substrate, particularly for the CNS which cannot use fat metabolism
- A decrease in blood glucose below 4-5mM is known as HYPOGLYCAEMIA, and may impair brain function
- A decrease in blood glucose below 2mM leads to unconsciousness, and perhaps coma and death

### *Feedback Loop*

- Increased blood glucose concentration
- Increased insulin secretion
- Decreased blood glucose concentration
- Increased secretion of:
  - Glucagon
  - Catecholamines
  - Somatotrophin
  - Cortisol

### The Pancreas

- Important in PATHOGENESIS of diabetes
- Approx 98% pancreatic tissue associated with EXOCRINE secretions via duct to small intestine
- The remaining 2% are known as ISLETS OF LANGERHANS and are clumps of cells with a specific ENDOCRINE function

### *Islets of Langerhans*

- 3 types of cells work together, each with specific endocrine function
  - Alpha; glucagon secretion
  - Beta; insulin secretion
  - Delta; somatostatin secretion
- PARACRINE control: the islets of Langerhans are cells that are very close together with small gaps between them. These gaps have high hormone concentrated fluids which allow communication between the cells. GAP JUNCTIONS allow small molecules to pass directly between cells, and TIGHT JUNCTIONS for small intercellular spaces.
- **Insulin**
  - stimulates growth and development in utero and child
  - decreases blood glucose (metabolic pathway)



- **Glucagon**
  - increases blood glucose
- **Somatostatin**
  - Inhibits insulin and glucagon- NEGATIVE HORMONE
  - Mainly paracrine effects

#### *Beta Cells*

- **Increased Blood glucose → insulin release**
- **Other stimulatory molecules:**
  - Alpha cells secrete glucagon
  - Certain GI hormones
  - Certain amino acids
  - Parasympathetic nervous activity (beta-receptors)
- **Inhibitory molecules:**
  - Sympathetic nervous activity (alpha-receptors)
  - Somatostatin
- **Increased insulin release →**
  - Increased GLYCOGENESIS
  - Increased GLYCOLYSIS
  - Increased GLUCOSE TRANSPORT into cells via GLUT4  
→ **Decreased blood glucose**
- **Other effects of insulin release:**
  - Increased amino acid transport
  - Increased protein synthesis
  - Decreased LIPOLYSIS
  - Increased LIPOGENESIS

#### *Alpha Cells*

- **Decreased Blood glucose → Glucagon release**
- **Other stimulatory molecules:**
  - Certain GI hormones
  - Certain amino acids
  - sympathetic nervous activity
- **Inhibitory molecules:**
  - Beta cells secrete insulin
  - parasympathetic nervous activity (alpha-receptors)
  - Somatostatin
- **Increased glucagon release →**
  - Increased HEPATIC GLYCOGENOLYSIS  
→ **Increased blood glucose**
- **Other effects of glucagon release:**
  - Increased amino acid transport into liver → increased GLUCONEOGENESIS → increased blood glucose
  - Increased lipolysis → increased gluconeogenesis → increased blood glucose

Glucokinase

- Also known as HEXOKINASE IV (glucose sensor)
- Glucose transported into beta cell via GLUT 2 (not insulin stimulated)
- Glucose is then converted to glucose-6-phosphate using Glucokinase, synthesising ATP
- Via metabolic pathways, G6P results in insulin synthesis and release from the beta-islet cell
- In rare cases of diabetes, e.g. MODY, glucokinase is missing in the patients

Insulin

- Formed from PROINSULIN; single amino acid chain joined by many disulphide bridges
- Pro- insulin is processed by the beta cell before release:
  - Cleaved at amino acid 64 and 32
  - Cleavage produces C-PEPTIDE and the ALPHA and BETA CHAINS of insulin
  - Disulphide bridges then lead to the specific 3D structure formation of insulin
- Processing of pro-insulin is impaired in T2DM, but is not the cause of T2DM. This means that patients will secrete pro-insulin.
- INSULINOMAS: tumour of pancreatic tissue secreting insulin and C-peptide (inappropriate release)
- Measurements of C-peptide can be used to assess PANCREATIC FUNCTION

Beta-cell function

- Glucose enters via GLUT-2
- Glucose  $\rightarrow$  G6P + ATP
- ATP blocks ATP sensitive K<sup>+</sup> channel
- Blocked channel  $\rightarrow$  opening of voltage gated Ca<sup>2+</sup> channel
- Influx of Ca<sup>2+</sup> into beta cell  $\rightarrow$ 
  - Released of PREFORMED insulin
  - Synthesis of NEW insulin
- Oral glucose insulin production > intravenous glucose insulin production

GLP-1

- Glucagon-like peptide 1
- GI hormone secreted in response to food
- Transcription product of PROGLUCAGON gene, primarily from L CELLS
- Causes increase in insulin release and a decrease in glucagon release
- Also causes an increase in SATIETY, therefore can be used to help weight loss
- However GLP-1 has a short half life, as it is broken down by DPPG-4
- T2DM treatment: injection of GLP-1 and DPPG-4 INHIBITOR, to increase the half life of GLP-1

Insulin Secretion

- BIPHASIC manner of secretion
- FIRST PHASE INSULIN: stored insulin which is released directly after a meal
- SECOND PHASE INSULIN: newly synthesised insulin which is released over a couple of hours, and increases food storage (glycogenesis)

*Receptor*

- 2 cytoplasmic alpha subunits- recognise and bind to insulin
- 2 transmembrane beta subunits with TYROSINE KINASE domains
- Binding of insulin → conformational change in tyrosine kinase domains
- Also AUTOPHOSPHORYLATION and CROSS-PHOSPHORYLATION of receptors occurs
- Conformation change → phosphorylation of cell protein substrates
- T2DM patients are INSULIN RESISTANT. Abnormality does not reside in the insulin receptor, but in the metabolic pathway of insulin action.

## Introduction to Diabetes Mellitus

Endo 5 - Dr Stephen Robinson ([Stephen.robinson@imperial.ac.uk](mailto:Stephen.robinson@imperial.ac.uk))

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1. List and describe the effects of insulin across intermediary metabolism
2. Describe and explain the metabolic changes in the fed and fasted state
3. List the principal signs and symptoms of diabetes mellitus, and relate them to the underlying pathophysiology.
4. Distinguish between Diabetes Mellitus types 1 and 2.
5. Explain the aetiology of type 1 diabetes mellitus.
6. Define insulin resistance and explain how it is related to diabetes, dyslipidaemia, hypertension and ischaemic heart disease
7. Describe the consequences of insulin resistance on glucose, lipid and protein metabolism
8. Describe the physiology and risks of obesity.
9. Describe the pathophysiology of type 2 diabetes

### Actions of Insulin

- Metabolic processes
  - Glucose; decrease HEPATIC GLUCOSE OUTPUT, and increase muscle glucose uptake
  - Protein; decrease PROTEOLYSIS
  - Lipid; decrease LIPOLYSIS and KETOGENESIS
- Growth: particularly in utero, but also in children
- Vascular effects: alters blood flow in certain tissues e.g. muscles
- Ovarian function: important in polycystic ovarian syndrome
- Clotting: PAI-1
- Energy expenditure: in relation to LEPTIN

### *Glut-4*

- Main insulin stimulated/responsive transporter
- Expressed in muscle and adipose tissues
- Lies in vesicles
- Recruited and enhanced by insulin
- Results in a 7x increase in glucose uptake into cells
- Consists of a hydrophobic outer layer and a hydrophobic core

*Proteins*

- Metabolism responsible for 20% of energy expenditure
- Insulin inhibits PROTEOLYSIS (GLUCONEOGENIC amino acids e.g. Alanine liberated from proteins); CORTISOL stimulates this
- Insulin, growth hormone and IGF1 stimulate PROTEIN SYNTHESIS (from amino acids)
- Insulin also inhibits the conversion of Oxygen to carbon dioxide

*Glucose*

- Present in blood at ALL times
- GLYCOGEN: stored glucose in HEPATOCYTES (liver cells), acting as an immediate energy store
- Effects of insulin:
  - Stimulates GLYCOGENESIS (the conversion of glucose to glycogen)
  - Inhibits GLUCONEOGENESIS (the conversion of glycogen to glucose). This is stimulated by GLUCAGON, CATECHOLAMINES and CORTISOL
  - Inhibits HEPATIC GLUCOSE OUTPUT (the release of glucose from the hepatocytes)
- Effects of Glucagon:
  - Increases uptake of gluconeogenic amino acids into cells
  - Stimulates GLYCOGENOLYSIS and GLUCONEOGENESIS
  - Increases hepatic glucose output

*Fuel Stores*

- **Carbohydrates**
  - Liver and muscle cells: glycogen → glucose (especially used in brain)
  - Short term source: 16 hrs
- **Protein**
  - Longer term: 15 days
- **Fat**
  - Long term source: 30-40 days
  - Highest energy released per gram

*Fat metabolism*

- Insulin and LIPOPROTEIN LIPASE stimulates the breakdown of TRICLYGERIDES into GLYCEROL and NON-ESTERIFIED FATTY ACIDS
- Insulin also stimulates the uptake of glucose into ADIPOSE tissue via Glut-4 transporter
- Effects of insulin WITHIN adipose tissue:
  - Stimulates the formation of triglycerides from GLYCEROL-3-PHOSPHATE and non-esterified fatty acids
  - Inhibits the breakdown of triglycerides into GLYCEROL and non-esterified fatty acids
- Catecholamines, cortisol and growth hormone stimulates the breakdown of triglycerides into GLYCEROL and non-esterified fatty acids

Omental circulation

- Via the HEPATIC PORTAL VEIN; heart → GI tract → liver → heart
- ADIPOCYTES in GI tract are highly metabolically active

- Increased waist circumference as a result of increased number of adipocytes in the GI tract leads to an increased risk of ischaemic heart disease and death

#### *Hepatic Gluconeogenesis*

- Occurs in the liver; hepatocytes
- Glycerol (in the blood) are taken up into the hepatocytes to form GLYCEROL-3-PHOSPHATE
- Glycerol-3-phosphate is readily interconverted to triglycerides
- Glycerol-3-phosphate is also readily converted into GLUCOSE (this is gluconeogenesis)
- Glucose is then released from the hepatocyte via hepatic glucose output (this is the cause of 25% of glucose output after a 10 hour fast)

#### *NB: the brain*

- Needs energy
- Can use glucose and ketone bodies as source of energy, but cannot use fatty acid metabolism
- This is because LIPOLYTIC ENZYMES are not present in the brain; suggested reasons for this is that lipolytic enzymes may degrade brain tissue

#### *Fatty acids in the liver*

- NON-ESTERIFIED fatty acids are taken up into hepatocytes, where they are converted to FATTY ACYL COA
- Fatty acyl CoA is then converted to Acetyl CoA → Acetoacetate → Acetone and 3 HYDROXYBUTARATE
- These are then released as KETONE BODIES (which are an alternative source of fuel for the brain if hypoglycaemia occurs)
- Insulin inhibits this process, and glycogen stimulates the conversion of fatty acyl CoA to ketone bodies
- Ketones in urine indicate fasting which has lead to fatty acid metabolism
- Elevated glucose and ketones present in urine is ABNORMAL and indicates INSULIN DEFICIENCY

#### *Hepatic Glycogenolysis*

- After glucose is taken up into hepatocytes and converted to GLUCOSE-6-PHOSPHATE, it is stored as glycogen
- Insulin stimulates the conversion of Glucose-6-phosphate into glycogen
- Glucagon and catecholamines inhibit this conversion, but stimulate the reverse
- Glucose-6-phosphate can also be re-converted to glucose, which can be released from the cell via HEPATIC GLUCOSE OUTPUT to increase the blood glucose levels

#### *Muscle Cells*

- Fatty acids are taken up into muscle cells where they are converted to acetyl CoA (which then enters the Krebs cycle)
- Glucose uptake
  - Via Glut-4
  - Stimulated by insulin
  - Inhibited by growth hormones, catecholamines and cortisol
- Glucose is then either stored as glycogen, or converted to acetyl-CoA (which then enters the Krebs cycle)

## The Fasted State

- Low insulin to glucagon ratio
- Blood glucose concentration is between 3.0-5.5 mM (this is a relatively fixed range due to the importance of glucose in brain function)
- Increased in non-esterified fatty acids within the blood
- Decrease in amino acids within the blood when prolonged

### *Prolonged fasting*

- Increase in proteolysis; amino acids released from muscles
- Increased lipolysis; adipocytes release glycerol and fatty acids
- Increased hepatic glucose output from Glycogenolysis and gluconeogenesis
- Muscles use lipid metabolism as energy store
- Brain use glucose metabolism, followed by ketone bodies
- Increased KETOGENESIS (formation of ketone bodies)

## The Fed State

- 1<sup>st</sup> phase insulin stored released
- 2<sup>nd</sup> phase (synthesised) insulin released slowly
- High insulin to glucagon ratio
- Hepatic glucose output stopped
- Increased glycogenesis
- Reduced gluconeogenesis and Glycogenolysis
- Increased protein synthesis
- Decreased proteolysis
- Increased lipogenesis (glycerol and fatty acids taken up by adipocytes → triglycerides)

## Type 1 Diabetes Mellitus

### *Presentation*

- Absolute insulin deficiency (due to abnormal/lack of pancreatic function)
- Increased hepatic glucose output; releasing glucose and ketones into the blood
- Increased proteolysis; releasing amino acids which leads to weight loss
- Increased lipolysis; releasing glycerol and fatty acids from adipocytes
- GLYCOSURIA with osmotic symptoms; increased glucose in urine → increased water in urine → dehydration → increased thirst
- KETONURIA: presence of ketone bodies in urine
- Treatment: insulin

### *Insulin induced hypoglycaemia*

- Treatment induced complication
- Increased insulin from SUBCUTANEOUS stores → glucose uptake into muscle → low plasma glucose concentration
- TREATMENT: Increased INTRAMUSCULAR glucagon → increased hepatic glucose output, Glycogenolysis and gluconeogenesis and increased lipolysis → increased plasma glucose

- Also catecholamines, cortisol and growth hormones act as a counter-regulatory system to increase plasma glucose during hypoglycaemia (same effects as glucagon)

## Type 2 Diabetes Mellitus

### *Insulin resistance*

- Resistance resides in liver, muscles and adipose tissue
- Seen in terms of glucose metabolism, fat metabolism and LIPOPROTEIN metabolism
- Leads to increase in circulating non-esterified fatty acids (as a result of adipocytes breaking down triglycerides)
- Lipoprotein metabolism effects:
  - Decrease in VLDL clearance
  - Increase in triglyceride formation
  - Decrease in HDL ("good cholesterol")
  - Increase in overall cholesterol
- Usually enough insulin to suppress ketogenesis and proteolysis
- **Other effects of insulin resistance**
  - Increased impaired glucose tolerance
  - Increase waist circumference (due to increased triglyceride formation)
  - Increased storage of OMENTAL fat
  - Increased HYPERTENSION
  - Increased ADIPOCYTOKINES
  - Changes in inflammatory state and energy expenditure also seen

### *Presentation*

- Effects of insulin resistance
- CENTRAL ADIPOSITY; 60-80% of patients are obese, especially with respect to omental fat
- DYSLIPIDAEMIA: A disorder of lipoprotein metabolism, including lipoprotein overproduction or deficiency. Dyslipidemias may be manifested by elevation of the total cholesterol, the "bad" low-density lipoprotein (LDL) cholesterol and the triglyceride concentrations, and a decrease in the "good" high-density lipoprotein (HDL) cholesterol concentration in the blood.
- HYPERGLYCAEMIA
- Later → insulin deficiency
- There are less osmotic symptoms (e.g. polyuria and polydipsia) than T1DM, but many complications involved

### *Diet*

- Important in T1 and T2
- Not specific; insulin treatment arranged as to respond to a healthy diet
- T2DM often suggests total calorie control
- Reduced number of fat calories
- Reduced refined carbohydrate calories
- Increased complex carbohydrate calories
- Increased soluble fibre – prolongs absorption of food therefore second phase insulin is also used
- Reduced sodium intake

# Tutorial 3: Diabetes Mellitus

Endo 5 - Professor K Meeran ([k.meeran@imperial.ac.uk](mailto:k.meeran@imperial.ac.uk))

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## Case History

### Case 1

A **23-year old** journalist presents with a **3-month history of weight loss**. She **drinks** up to 3.5 litres (water, tea, lemonade) a day and passes **similar volumes of urine**, and wakes up at night three times to pass urine. There are **no abnormal physical signs**. Her urine has **++++ of glucose and ketones**. **Capillary glucose was 23 mmol/l**.

## Notes

- Age: 23 yr old
- Polydipsia
- Polyuria
- Age < 30 yrs – T1DM, even though increase in prevalence of obesity has led to earlier development of T2DM
- 3 month history – rapid onset; more typical of T1
- No abnormal physical signs – more typical of T2, but can be T1 as well
- ++++ glucose & ketones – urine DIP STICK test
  - No ketones = yellow
  - Ketones = green
  - ++++ = completely green (+ is a scale of ketone presence in urine)
  - T2DM – ketones not present in urine unless fasting
  - This suggests lack of insulin = T1DM; GAD antibodies wipe out beta islets in pancreas
- CG 23 mmol/l – hyperglycaemic
- Role of insulin: activates-
  - GLUT 2
  - GLUT 4
  - Glycogen synthase

## Questions:

1. **What is the diagnosis?**
  - Type 1 diabetes mellitus
2. **Why does she have glucose in her urine and why is she passing so much urine?**
  - Lack of insulin – glucose uptake (via Glut 2 and glut 4) stopped, glycogenesis does not occur (glucose → glycogen) therefore glucose remains in the plasma and is passed out in the urine
  - Increased glucose concentration in the urine exerts an increased osmotic pressure, therefore more water is drawn out into the urine (due to increased osmolarity) therefore urine volume increases
3. **Why is her plasma glucose high and what would her plasma insulin concentration be if we measured it (but no need clinically)?**
  - T1DM – beta islets wiped out by GAD antibodies, therefore no insulin synthesised or secreted
  - Therefore plasma insulin concentration would be 0 mmol/l



**Case 2**

A **58 year old** bus driver presents with **angina pectoris** due to **coronary artery disease**. He is **overweight** (Body Mass Index, **BMI = 32 kg/m<sup>2</sup>**). During investigation he is found to have a fasting **plasma glucose of 12 mmol/l** (normal FPG < 6.0 mmol/l). He is started on a diet for his diabetes

Notes:

Angina pectoris – chest pain during activity

Questions:

1. **What is the diagnosis and what (if we bother to measure it) is his plasma insulin concentration likely to be?**
  - Type 2 diabetes mellitus
  - Plasma insulin concentration likely to be normal/high
    - Not caused by lack of insulin, but unresponsiveness to insulin
    - Body tries to compensate by increasing insulin secretion, but no effect
  
2. **What are the important features of his diet? How does energy restriction help?**
  - Overall calorie control:
    - Reduce fat calories
    - Reduce refined carbohydrate calories
    - Increase complex carbohydrate calories
    - Increase soluble fibre
    - Reduce sodium intake
  - Energy restriction will ensure that glucose is taken up into cells as a necessary energy source, therefore preventing hyperglycaemia
  
3. **Other advice to reduce chance of morbidity?**
  - Physical activity and weight loss
  - Obesity increases complications associated with T2DM

## The thyroid gland & the iodothyronines

Endo 6 - Professor John Laycock ([j.laycock@imperial.ac.uk](mailto:j.laycock@imperial.ac.uk))

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1. Describe the anatomy of the thyroid and the structure of the follicles.
2. List the main hormones produced by the follicular and parafollicular cells of the thyroid.
3. Describe by means of a labelled diagram the principal features of iodothyronine synthesis, storage and release.
4. Describe the physiological actions of the iodothyronines.
5. Explain the mechanism(s) of action of the iodothyronines.
6. Describe the control mechanisms of iodothyronine production with particular reference to the hypothalamo-pituitary-thyroidal axis.
7. Describe the principal clinical effects of excess circulating iodothyronines, and name the condition described.
8. Describe the principal clinical effects associated with a deficiency in circulating iodothyronines, and name the condition described.
9. Understand the principles of treatment issues in the individual patient.

## The Thyroid Gland

- Develops from the base of the pharynx
- Consists of the thyroid and parathyroid glands (which secrete PARATHYROID hormone; PTH)
- 2 main lobes, and sits just above the trachea
- Gland consists of FOLLICLES
  - Circular formation of FOLLICULAR cells surrounding the antral mass known as the COLLOID (proteinaceous yellow jelly-like fluid)
  - PARAFOLLICULAR cells lie outside the follicle, and secrete CALCITONIN

### *Iodine*

- Iodine enters the body via the GI tract as iodide
- Iodide (I<sup>-</sup>) then circulates in the blood, where it is transported to the BASOLATERAL membrane of the follicular cells in the thyroid
- The concentration of iodide in the cells is 25x the concentration of iodide in the blood, but it is taken up into the follicular cell by specific NIS IODIDE PUMPS
  - Iodide has a negative charge (I<sup>-</sup>), therefore its uptake creates an ELECTROCHEMICAL GRADIENT whereby further iodide uptake is repelled by the negative charge of the intracellular fluid.
  - The pumps therefore require energy to transport iodide from the blood into the cell, which is obtained by COUPLING the transport with Na<sup>+</sup> transport
  - THYROTROPHIN/THYROID STIMULATING HORMONE (TSH) regulates this uptake; there are specific TSH receptors on the basolateral membrane of the follicular cell
- PENDRIN IODIDE PUMPS on the APICAL membrane of the pump the iodide from the follicular cells into the COLLOID
  - TSH regulates the activity of the pendrin pumps too

### *Thyrotrophin/ Thyroid Stimulating Hormone (TSH)*

- Stimulates the synthesis of THYROGLOBULIN (TG)
  - This is specific to follicular cells
- TG then moves through the APICAL membrane into the colloid
- TG stimulates THYROIDAL PEROXIDASE (TRANSMEMBRANE enzyme which works in conjunction with HYDROGEN PEROXIDE) to convert:
  - IODINE → REACTIVE IODINE
  - This is known as IODINATION

### *Thyroglobulin (TG)*

- Globular protein
- Long chain of amino acids consisting of many TYROSINES; known as TYROSYL RESIDUES
- Reactive iodine incorporates into the tyrosyl residues
- This stimulates the DI-IODYLYTYROSYL (DIT) and MONOIODOTYROSYL (MIT) process

### *Thyroidal Peroxidase*

- Enzyme which catalyses the COUPLING of DIT and MIT, by altering the configuration of their amino acid chains
- Products:

- 3,5,5- TRI IODOTHYRONINE (T3)
- 3,5,3,5- TETRA IODOTHYRONINE (T4)
- These are polypeptide hormones which are stored in the colloid attached to TG
- T4 is also known as THYROXINE

#### *Other role of TSH*

- Stimulates the migration of lysosomes to the APICAL membrane of the follicular cells
- T3 and T4 are then taken up from the colloid into the cell by ENDOCYTOSIS
- T3 and T4 then fuse with the lysosome:
  - this breaks down the TG into amino acids
  - releases iodine
  - releases T3 and T4, which are then expelled into the bloodstream

#### Iodothyronines

- Consist of T3 and T4
- Transported in the blood
- Mostly bound to plasma proteins
- Plasma protein component acts as store of iodothyronines
- Dynamic Equilibrium reached between free hormone and protein-bound hormone levels within the blood
- Unbound hormones are BIOACTIVE, but only 0.05% of T4 and 0.5% of T3 exist as unbound hormones

#### *Plasma Proteins*

- **TBG (thyronin-binding globulin)**
  - Specific to T3 and T4
  - High affinity, low capacity
  - 70% T4, 80% T3 exist bound to this protein
- **Albumin**
  - Non specific
  - Low affinity, high capacity
  - 20% T4, 10% T3 exist bound to this protein
- **Pre-albumin**
  - Also known as TRANSTHYRETIN
  - 10% T4, 10% T3 exist bound to this protein

#### *Latent Periods & Half Life*

- Latent period:
  - T3 and T4 have a very long time period before effect
  - T3 around 12 hrs
  - T4 around 72 hrs
- Biological Half-life:
  - T3 around 2 days
  - T4 around 7-9 days

*Deiodination of T4 (THYROXINE)*

- T4 is the main product of the thyroid gland
- In target tissues, it is mostly DEIODINATED to the more bioactive T3
- It can also be deiodinated in a DIFFERENT position to the biologically INACTIVE molecule known as REVERSE T3 (r-T3)

Main actions of the Iodothyronines

- **Increase Basal metabolic rate (BMR)**
  - In most peripheral tissues (mostly by maintaining Na<sup>+</sup> pumps)
  - Increase CALORIGENESIS (although not in brain)
  - Secondary effect: heat production, therefore THERMOREGULATION
  -
- **Increase Protein, Carbohydrate and Fat Metabolism**
  - Both ANABOLIC and CATABOLIC metabolism
  - Overall effect depends on the general thyroid status
  - Important for normal growth and development
    - Especially foetal growth and development (both physical/body and brain)
    - CRETINISM; condition as a result of absent T3 and T4 during foetal development → lack of mental and physical development
- **Potentiate actions of the Catecholamines**
  - E.g. tachycardia, Glycogenolysis, lipolysis
  - Interaction between iodothyronines and the SYMPATHETIC nervous system
  - Conditions can be treated with beta-blockers
- **Interaction with other Endocrine systems**
  - E.g. oestrogens
- **Effect on the CNS**
  - E.g. normal mentation, myelination of neurones etc
- **Increase vitamin A and retinal synthesis**

*Mechanisms of Action*

- In the blood, primarily T4 (but T3 also present)
- Hormones enter target cell, where T4 is converted to T3
- T3 is the CELLULAR BIOACTIVE MOLECULE
- Main mechanism: GENOMIC
  - Binds to TR receptor on nucleus
  - Stimulates transcription
  - Increases protein synthesis
- Other possible mechanisms
  - Increase membrane transport mechanisms
  - Increase metabolic activity in mitochondria

## Control of Iodothyronine Production

- Hypothalamus releases TRH (thyrotrophin releasing hormone)
- Anterior pituitary (adenohypophysis) releases THYROTROPHIN/TSH (thyroid stimulating hormone)
- Thyroid gland releases IODOTHYRONINES (T3 and T4)

### *Negative Feedback*

- Thyrotrophin release from the anterior pituitary has an AUTO INHIBITION of the hypothalamus, so TRH is not released
- Iodothyronines released from the thyroid also have negative feedback loops:
  - They have a DIRECT INHIBITION of the TRH release from the anterior pituitary
  - INDIRECT INHIBITION of the hypothalamus, so TRH is not released
- Other possible effects:
  - Somatostatin inhibits TRH release from the adenohypophysis
  - Oestrogen STIMULATES TRH release
  - Glucocorticoids inhibits TRH release
  - Sympathetic innervations of the thyroid inhibits iodothyronine release
  - Inorganic iodide (WOLFF-CHAIKOFF EFFECT) inhibits iodothyroning release

### *Thyrostimulin*

- 2 unit glycoprotein
- Found in anterior pituitary (As well as other tissues)
- Binds to thyrotrophin (TSH) receptor
- Functions unknown, but possibly regulatory mechanism of Thyrotrophin release

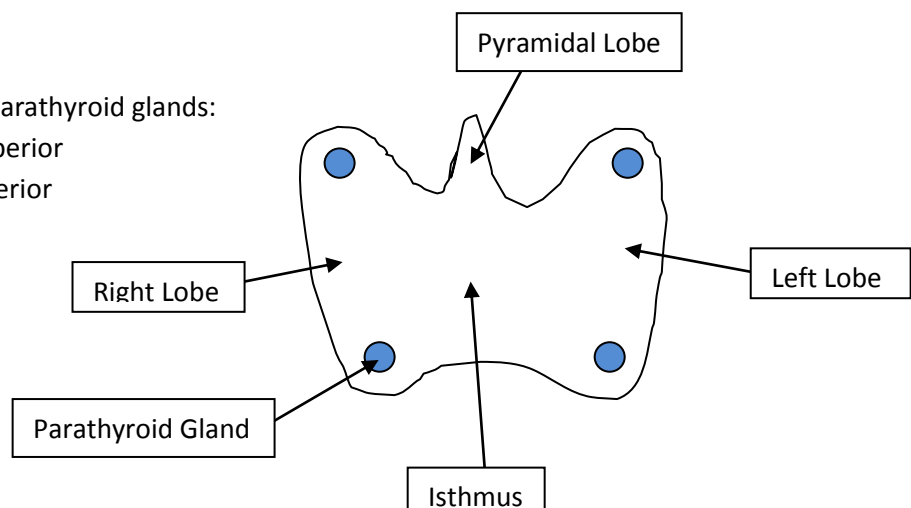
## General Thyroid Disorders

Endo 7 - Dr Karim Meeran [k.meeran@imperial.ac.uk](mailto:k.meeran@imperial.ac.uk)

1. Describe the anatomy of the thyroid and the structure of the follicles.
2. List the main hormones produced by the follicular and parafollicular cells of the thyroid.

### Anatomy of the Thyroid

- In the neck
- Shield shaped
- Embedded within are 4 parathyroid glands:
  - Right and left superior
  - Right and left inferior
- The parathyroid glands consist of different cells and are important in Ca metabolism



### *Embryology*

- Origin: back of the tongue
- Development starts in utero after 7 weeks, where a midline outpouching forms of the floor of the pharynx
- The outpouching then forms a duct known as the THYROGLOSSAL duct and elongates down
- The duct migrates down the neck and divides into two lobes
- Reaches final position by week 7, where the duct disappears leaving dimple in tongue known as the FORAMEN CAECUM
- Thyroid gland then develops

### Structure

- Adult weight = 20g
- Each lobe = 4x2.5.2.5 cm
- Consists of 4 lobes:
  - Right lobe
  - Left lobe
  - Isthmus
  - Pyramidal lobe (occasionally; remnant of thyroglossal duct)
- Right lobe > left lobe
- Embedded parathyroid glands
- Left recurrent laryngeal nerve runs close to the gland; vocal cord supply

### *Recurrent laryngeal nerve*

- Damage can cause changes in quality of voice, or even difficulty talking
- Thus all thyroid surgeons mention this when obtaining consent for THYROIDECTOMY

### Problems with development

- **Agensis** – complete absence
- **Incomplete descent** – from base of tongue to trachea
  - Lingual thyroid – complete failure to descend from base of tongue
- **Thyroglossal cyst** – segment of duct persists and presents as lump years later

### *Thyroxine*

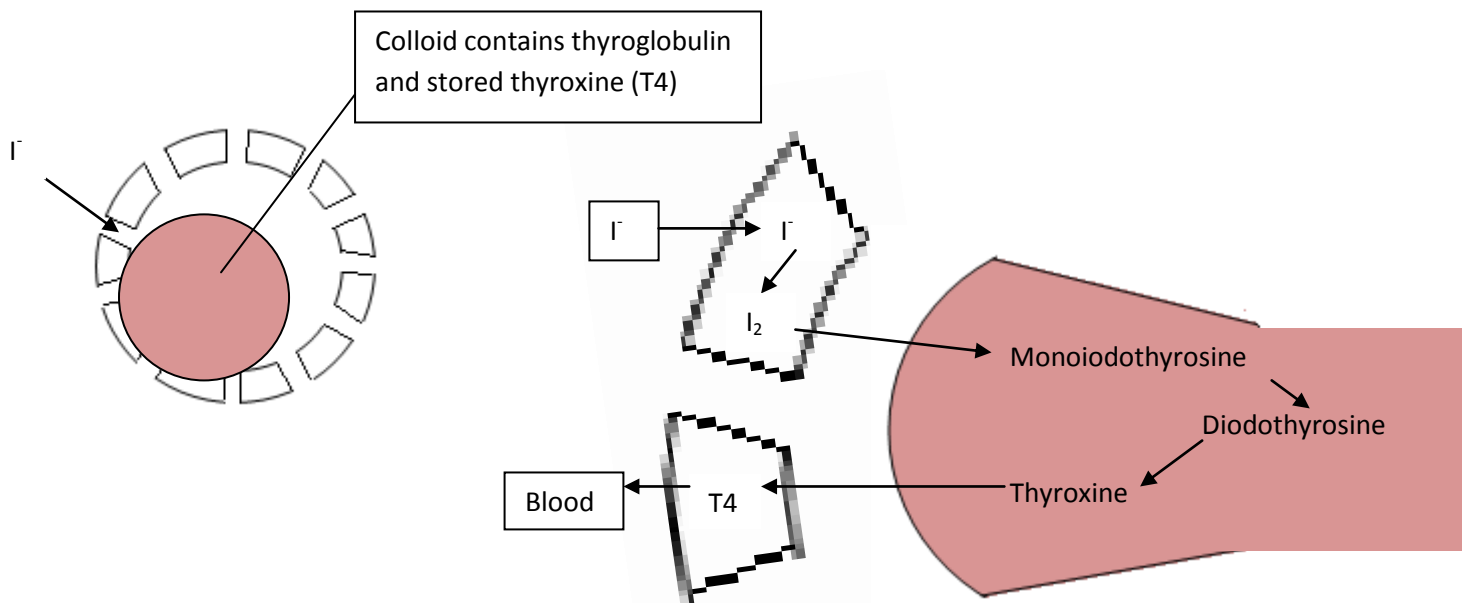
- Essential for normal brain development
- Controls cellular activity
- Neonates with deficiency in utero have irreversible brain damage = CRETIN

### *Cretinism*

- Cretin – an individual with irreversible brain damage caused by lack of thyroxine
  - Mentally sub-normal
  - Short stature
- Cretinism prevention – babies at 5-10 days have heel prick blood test
  - Thyroid function – measures TSH; if TSH is high thyroxine is given immediately
  - Guthrie test – tests for phenylketonuria

### Thyroid Follicular Cell

- Site of thyroxine synthesis (see previous lecture)
- Also known as Thyrocyte
- Thyroxine controls BMR
- Thyroxine binding globulin binds 75% of thyroxine in the circulation (NOT THYROGLOBULIN – this is present in the thyroid gland)
- The thyroid gland is normally responsible for synthesis, storage and secretion of thyroid hormones
  - Thyroid hormones regulate growth, development and BMR



### Thyroid Disease

- Affects 5% of the population
- Female: male = 4:1
- Overactive: underactive = 1:1

#### Primary Hypothyroidism – MYXOEDEMA

- Caused by autoimmune damage to the thyroid, or surgical removal
- Underactive thyroid gland
- Primary thyroid failure → decline in thyroxine secretion by thyroid gland
- Anterior pituitary gland detects this fall and secretes TSH (thyroid stimulating hormone)
- Normal HPT axis: hypothalamus secretes TRH (thyrotrophin releasing hormone), stimulates anterior pituitary to secrete TSH, which stimulates thyroxine release from the thyroid.
  - Thyroxine release then exerts a negative feedback effect on both the hypothalamus and the anterior pituitary
- FEATURES:
  - Decrease BMR
  - Deepening voice – larynx vibrates more slowly
  - Depression and tiredness
  - Cold intolerance

- Weight gain with reduced appetite
- Constipation
- Bradycardia (Heart rate < 60bpm)
- Eventual myxoedema coma
- TREATMENT – essential
  - If not treated, cholesterol increases causing death from MI/stroke
  - Thyroxine replacement (usually one 100microgram tablet daily)
  - Also monitor TSH levels and adjust thyroxine dose until TSH normal

#### *Primary Hyperthyroidism – THYROTOXICOSIS*

- Overactive thyroid gland makes too much thyroxine
- TSH levels fall to 0
- Increases BMR
- Increases body temperature
- Weight loss due to increased calorie burning
- Tachycardia (heart rate >100 bpm)
- Increase metabolic rate of all cells
- FEATURES:
  - Mood swings – irritable, short-tempered
  - Restless
  - Sleep difficulties
  - Feeling hot in all weather
  - Diarrhoea
  - Increased appetite but weight loss
  - Tremor of hands
  - Tiredness and myopathy
  - Palpitations
  - Sore eyes- trouble focussing, irritation, sensitivity
  - Enlarged thyroid – GOITRE
- CAUSES: GRAVES'S DISEASE
  - Whole gland is smoothly enlarged and the whole gland is overactive
  - Systemic disease of the whole gland
  - Autoimmune – antibodies bind to and stimulate the TSH receptors in the thyroid, stimulating thyroxine release
  - Leads to goitre and hyperthyroidism
  - Other antibodies bind to muscles behind the eye, causing muscle hypertrophy and EXOPHTHALMOS (swollen eye)
  - Other antibodies stimulate the growth of the shins and cause PRETIBIAL MYXOEDEMA – the non-pitting swelling that occurs on the shins (hypertrophy; growth of soft tissue)

## Tutorial 4: Thyroid Disorders

Endo 7 - Professor K Meeran ([k.meeran@imperial.ac.uk](mailto:k.meeran@imperial.ac.uk))

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### Case History

#### **Case 1**



A 25-year old lady who had recently undergone a divorce presented to her GP. She was upset about this and wanted something to calm her down and help her to sleep. She had been very irritable for the last 18 months. On direct questioning she admitted to a history of palpitations, weight loss and sweating over the past year. Two aunts had previously undergone neck operations and she had noticed a swelling in her own neck over the past year.

On examination she had a fine tremor and looked thin. Her pulse was 112 beats per minute and her blood pressure 106/70mm Hg. She had a swelling in her neck which moved with swallowing. It was soft, extended symmetrically either side of the midline and was not tender to the touch. Her GP sent off a blood sample to the hospital to obtain measures of thyroid activity.

### Case 2

A 32-year old woman presented to her GP with progressive tiredness over the last 2 years since the birth of her daughter. She wanted a vitamin preparation to give her more energy. She had been let go from her job as a cashier in her local supermarket 6 months earlier because her throughput of customers had slowed down so much. On direct questioning, she admitted to being constipated, intolerant of the cold and one stone heavier than before the birth of her child. Her periods were now much heavier and lasted longer than ever. There was no illness other than ischaemic heart disease in her family.

On examination she was pale, had an increased Body Mass Index (BMI) and appeared disinterested in her GP's questions. Her pulse was 54 beats per minute, and her blood pressure 110/75 mm Hg. She had slow relaxing reflexes but there were no other abnormal findings on examination. Her GP sent off a blood sample to the hospital to obtain measures of thyroid activity.

- Normal pulse: 60-100 beats per minute
  - Tachycardia > 100bpm
  - Bradycardia <60 bpm

### Hypothyroidism:

Secondary hypothyroidism is caused by TSH (thyrotrophin) deficiency

#### *Causes of hypothyroidism:*

- Surgery (thyroidectomy)
- Autoimmune disease – antibodies bind to TSH, therefore stimulating release
- Resistance to TSH
- Iodine deficiency

### Hyperthyroidism:

#### *Causes of hyperthyroidism:*

- Autoimmune disease (Graves' disease)
- Cancer: a TRH producing tumour in the hypothalamus; a TSH producing tumour in the hypophysis

#### *Mechanism of the effects of hyperthyroidism:*

- Thyroid hormones cause sensitisation to catecholamines
- This leads to tachycardia and increased sweat production

#### *Treatment of hyperthyroidism:*

- PTU: stops thyroxine production
- Radiolabelled iodine (131-I): destroys part of the thyroid gland
- Carbimazole: treatment of symptoms of hyperthyroidism

Questions:

1. **Which of the patients above has a) an overactive and b) an underactive thyroid. Indicate the likely results of thyroid function testing in each case.**
  - Patient 1 has an overactive thyroid – hyperthyroidism
    - Thyroid function test would show increased TSH levels, but TRH levels would be virtually zero
  - Patient 2 has an underactive thyroid – hypothyroidism
    - Thyroid function test would show reduced TSH levels, with increased TRH levels
2. **Outline the key clinical features that suggest the diagnosis of underactive and overactive thyroid disease in each case.**

This is self-explanatory.
3. **What anatomical structures are likely to be affected by an enlarged thyroid gland?**
  - The left recurrent pharyngeal nerve: this innervates the larynx and therefore there may a change in the quality of voice or difficulty in speaking
  - Trachea: there may be difficulty in breathing
  - Oesophagus: there may difficulty in swallowing

## The Adrenals and their hormones

Endo 8 - Professor John Laycock ([j.laycock@imperial.ac.uk](mailto:j.laycock@imperial.ac.uk))

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1. Describe the anatomy of the adrenal gland, identifying the medulla and the cortical zones.
2. List the main hormonal products from the adrenal medulla and the adrenal cortex.
3. Draw simple pathways identifying the main intermediates in the synthesis of the adrenal steroids.
4. State that the adrenal steroids exert their main effects via intracellular receptors and genomic mechanisms.
5. Identify the main mineralocorticoid in humans and describe its principal actions.
6. Describe the control mechanisms for mineralocorticoid hormones.
7. Identify the main glucocorticoid in humans and describe its principal actions.
8. State that cortisol plays an important role in the endocrine response to stress.
9. Describe the principal features of the hypothalamo-pituitary-adrenal axis.
10. State that adrenal androgen production in women can be clinically important in conditions of overproduction.
11. Describe the effects of excess and deficiency of cortisol.
12. Understand the principles of treatment issues in the individual patient.
13. Recognise the necessity for adrenal steroids for survival.

### The Adrenal Gland

- The adrenal glands lie on top of the kidneys, and consist of:
  - The adrenal medulla – core of the gland
  - The adrenal cortex – outer layers surrounding the core
- The adrenal cortex consists of 3 layers, known as CORTICAL ZONES:
  - Outer layer: Zona GLOMERULOSA
  - Middle layer: Zona FASCICULATA
  - Inner layer: Zona RETICULARIS
- The adrenal gland is then finally surrounded by a CAPSULE

- Functionally, the medulla and cortex act as separate endocrine glands, as they are involved with the synthesis and release of different hormones:
  - Medulla – CATECHOLAMINES
  - Cortex – CORTICOSTEROIDS

### *Cortical Zones*

- Arterial blood supply flows below the capsule surrounding the gland
- There are then two ways that blood is transported through the different cortical zones to the medulla:
  - Blood perfuse through cells until it reaches the TRIBUTARY OF CENTRAL VEIN in the centre of the medulla
  - Clearly defined ARTERIOLES flow from the outer capsule to the medulla
- The three cortical zones are layers of different cells that have grouped together:
  - Zona fasciculata – recognisable form; lines of cells which run towards the zona reticularis
  - zona reticularis and zona glomerulosa – no distinguishable form of cells
- the cortical zones release corticosteroid hormones

### *Medulla*

- made up of CHROMAFFINE cells
- cells synthesise and release Catecholamines
- catecholamines are polypeptide hormones synthesised from a TYROSINE precursor

### Adrenal Hormones

#### ➤ **Catecholamines**

- Released by the medulla
- 80% ADRENALINE (also known as epinephrine)
- 20% NORADRENALINE (also norepinephrine)
- Dopamine is also an end point of synthesis of catecholamines

#### ➤ **Corticosteroids**

- Released by the cortex
- Divided according to principal functions:
  - MINERALOCORTICIDS – aldosterone principal human hormone
  - GLUCOCORTICIDS – principally cortisol
  - SEX STEROIDS – androgens (oestrogens then synthesised from androgen precursor)
- Note: the zona glomerulosa is the only zone with the necessary enzyme for ALDOSTERONE synthesis, whereas the zona fasciculata and reticularis are both involved in the synthesis of cortisol, androgens and oestrogen

### Corticosteroids

#### *Steroid hormones*

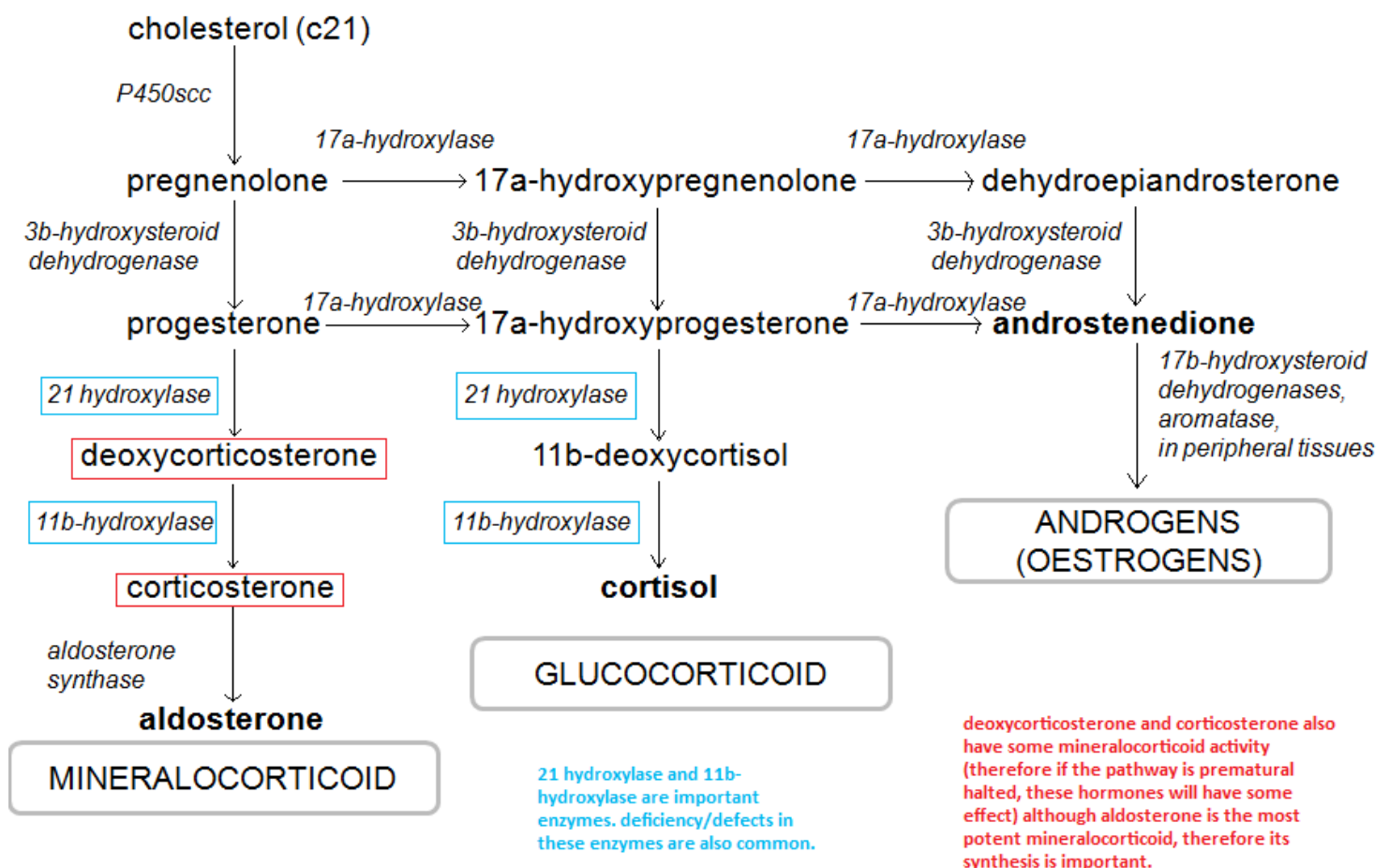
- All synthesised from the common precursor = cholesterol
- The adrenals are responsible for the synthesis and release of:
  - Mineralocorticoids (C21)
  - Glucocorticoids (C21)
  - (androgens)

- The Gonads are then responsible for the synthesis and release of:
  - o Progesterone (C21)
  - o Androgens (C19)
  - o Oestrogens (C18)

*Corticosteroid transport in blood*

- Corticosteroids are LIPOPHILIC, therefore can easily cross cell membranes where they bind with intracellular or nuclear membrane receptors
- Therefore these hormones cannot be stored, as this will result in excessive binding with receptors and hence over stimulation
- Because of this, the hormones can be produced on demand, or bound to plasma proteins in the blood to prevent their action
  - o The plasma proteins act as a store and transport mechanism – they transport the hormone where the unbound-bound hormone equilibrium is unbalanced, i.e. where the hormone needs to be released
- **Cortisol:**
  - o 75% bound to CBG (cortisol binding globulin – also known as TRANSCORTIN)
  - o 15% bound to the non-specific protein ALBUMIN
  - o 10% of the hormone is unbound, and is BIOACTIVE
- **Aldosterone:**
  - o 60% bound to CBG
  - o 40% unbound bioactive form

*Synthesis Pathways*



*Circulating concentration*

- Cortisol – controlled by the HYPOTHALAMO-PITUITARY axis, and is released in PULSES, which vary depending on time of day. This is known as CIRCADIAN RHYTHM:
  - 8am 140 – 690 **nmol/l**
  - 4pm 80 – 330 **nmol/l**
- Aldosterones – released in pulses, and depend on body positioning
  - Upright 140 – 560 **pmol/l**
- Note: cortisol is measured in nanomoles/l, whereas aldosterone is measured in picomoles/l
  - Nanomoles are 1000x greater than picomoles

Aldosterone

- stimulates **Na<sup>+</sup> reabsorption** in distal convoluted tubule and cortical collecting duct (and in sweat glands, gastric glands, colon)
- stimulates **K<sup>+</sup> and H<sup>+</sup> secretion**, also in distal convoluted tubule and cortical collecting duct. This is the only physiological way of removing potassium from the body

*Mechanism of action*

(Considering the distal convoluted tubule)

- Aldosterone diffuses into the distal convoluted tubule from the blood
- It then binds with an INTRACELLULAR receptor within the cell; MINERALOCORTICOID receptor (MR)
- The receptor-hormone complex is then transported into the nucleus, where it binds to specific DNA
- This activates transcription, translation and synthesis of specific proteins
- The proteins then act as:
  - ION CHANNELS – in the APICAL membrane, allowing Na<sup>+</sup> to be reabsorbed into the distal convoluted tubule from the TUBULAR FLUID
  - ION PUMPS – on the BASOLATERAL membrane, pumping Na<sup>+</sup> into the blood from the distal convoluted tubule, completing the reabsorption

*The Juxtaglomerular Apparatus*

- Aldosterone activity is tied to the structure of kidney NEPHRONS
- Overview of structure of a kidney nephron:
  - Glomerulus – proximal convoluted tubule -- loop of Henle (descending – ascending) – distal convoluted tubule – collecting duct
- Overview of blood supply to the nephron:
  - Afferent arteriole – blood to glomerulus – efferent arteriole – blood to general circulation
  - The afferent arteriole is adjacent to the point where the ascending loop of Henle meets the distal convoluted tubule
  - This is also in close proximity to the GLOMERULUS
- The smooth muscle in the wall of the RENAL AFFERENT ARTERIOLE has many secretory JUXTAGLOMERULAR cells which contain lots of secretory granules
  - The granules contain the enzyme RENIN (not rennin – different enzyme)
- MACULA Densa cells are part of the ASCENDING LOOP OF HENLE, and are adjacent to the juxtaglomerular cells
  - They are effectively specialised Na<sup>+</sup> sensors
- The juxtaglomerular apparatus describes the combination of the juxtaglomerular and macula densa cells.

*Renin release*

Three factors influence renin release from the juxtaglomerula cells in the distal convoluted tubule:

- **Decreased renal perfusion pressure**
  - This is associated with a decrease in arteriole blood pressure
- **Increased renal sympathetic activity**
  - As a result of trying to increase blood pressure
  - This directly activates the juxtaglomerular cells leading to renin release
- **Decreased Na<sup>+</sup> loads to top of loop of Henle**
  - This is recognised by the Na<sup>+</sup> sensing macula densa cells, which leads to increased renin release

*Renin – Angiotensin – Aldosterone System*

- Liver is the source of another plasma protein – ANGIOTENSINOGEN
- When the juxtaglomerular cells of the renal afferent arteriole secrete RENIN, this breaks off a peptide from angiotensinogen to form ANGIOTENSIN I
- Angiotensin I is then converted by ACE (ANGIOTENSIN CONVERTER ENZYME) to form ANGIOTENSIN II
- **Effects of angiotensin II:**
  - Vasoconstriction
  - Stimulates the ZONA GLOMERULUS of the adrenal cortex to synthesise and release ALDOSTERONE.
- This leads to increased Na<sup>+</sup> reabsorption in the distal convoluted tubule, therefore increasing water reabsorption which in turn increases the volume of the ECF (blood) – increasing BP
  - Chronic EC fluid increase can lead to high blood pressure; HYPERTENSION, therefore ACE inhibitors are main ANTIHYPERTENSIVES used
  - Corticotrophin (released from the anterior pituitary gland) also stimulates aldosterone release
  - Increased K<sup>+</sup> and decreased Na<sup>+</sup> also stimulates aldosterone release

Cortisol*Physiological Actions – Normal Stress Response*

- **Metabolic Effects**
  - Peripheral protein catabolism
  - Hepatic gluconeogenesis
  - Increased blood glucose concentration
  - Lypolysis in adipose tissue
  - Enhanced effects of glucagon and catecholamines
- **Mineralocorticoid effects**
  - Some, not major
- **Renal and Cardiovascular Effects**
  - Excretion of water load
  - Increased vascular permeability
- **Other effects**
  - Bone growth
  - CNS effects

### *Pharmacological effects of large amounts of cortisol*

- **Anti-inflammatory action**
- **Immunosuppressive action**
- **Anti-allergic action**

All of these are associated with decreased production of molecules such as prostaglandins, leukotrienes, histamine, etc. as well as on the movement and function of leukocytes and the production of interleukins

### *Cortisol Receptors*

- Two receptors will bind to cortisol with equal affinity:
  - GLUCOCORTICOID RECEPTORS
  - ALDOSTERONE (mineralocorticoid) RECEPTORS – aldosterone also binds to this receptor, therefore since two hormones bind to the same receptor, there is the potential of excessive receptor activity
- To prevent excess mineralocorticoid receptor activation in the kidney, BIOACTIVE cortisol is converted to BIOLOGICALLY INACTIVE CORTISONE
  - This involves **11 $\beta$ -hydroxysteroid dehydrogenase 2**

### Mechanism of Action

- Similar to aldosterone
- Cortisol binds to intracellular receptor, and the complex is transported to the nucleus where it binds to DNA stimulating protein synthesis
- E.g. ANNEXIN 1 and ANNEXIN 1 RECEPTOR are synthesised
  - The annexin 1 then exhibits AUTOCRINE action, preventing PROSTAGLANDIN synthesis via ARACHIDONIC ACID

### *Control of Cortisol*

- Principally via CORTICOTROPHIN (ACTH)
  - Released from the anterior pituitary gland
  - Precursor is POMC
- Corticotrophin- releasing hormone (CRH), and Vasopressin are control hormones released by the hypothalamus, which control the release of corticotrophin
- **Stimulation:**
  - Stressors via brain nerve pathway and circadian rhythm (biological clock) stimulate the release of CRH and vasopressin from the hypothalamus, therefore increasing cortisol (and small amounts of androgen) release
- **Inhibition:**
  - The release of corticotrophin from the anterior pituitary gland has a SHORT AUTONEGATIVE feedback loop with the hypothalamus, inhibiting CRH and vasopressin release
  - The release of cortisol has two negative feedback loops:
    - DIRECT NEGATIVE feedback to the anterior pituitary, inhibiting corticotrophin release
    - INDIRECT NEGATIVE feedback to the hypothalamus, inhibiting CRH and vasopressin release

### De-hydro-epi-androsterone (DHEA)

- Precursor for androgens and oestrogens

- Converted to active hormones within target cells (which have the appropriate enzymes)
- Peak serum levels at 20-30 years, then decrease steadily with increasing age
- Particularly important in postmenopausal women as precursor for oestrogen (and androgen) synthesis by target tissues in the absence of ovarian steroids

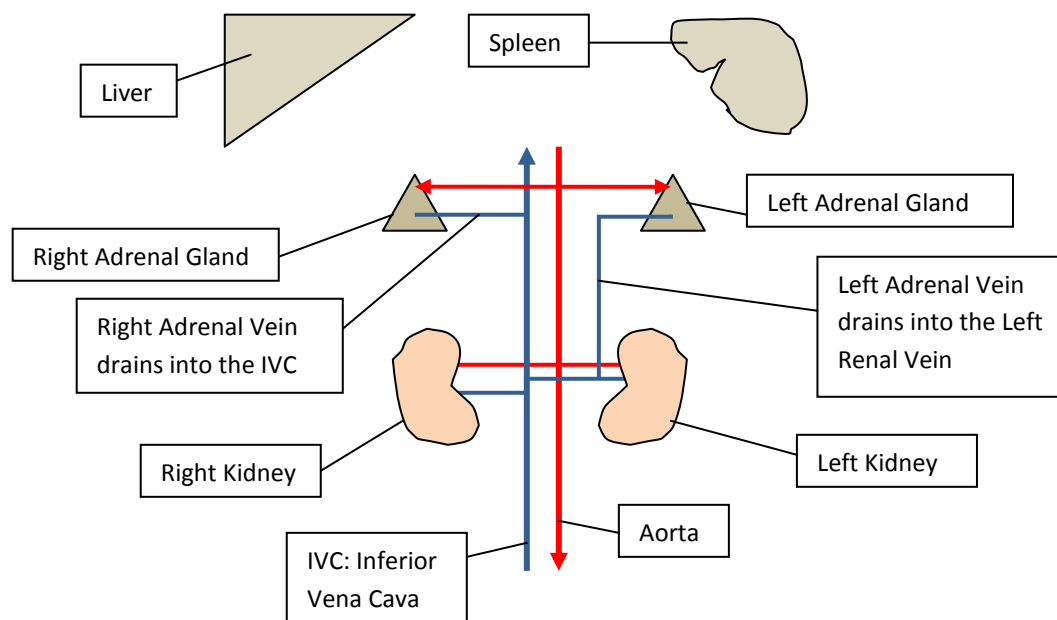
## Adrenal Disorders

Endo 9 - Dr Karim Meeran ([k.meeran@imperial.ac.uk](mailto:k.meeran@imperial.ac.uk))

### Endocrine Diseases

- Syndromes of excess/deficiency of hormone messengers
- Adrenal failure = Addison's
- Excess cortisol = Cushing's

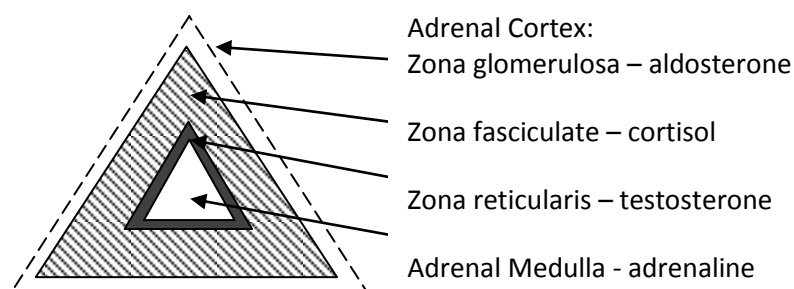
### Anatomy of the adrenals



- Both adrenals have many arteries/arterioles, but only one vein.
- Spleen is at risk with a left ADRENALECTOMY – therefore immunise with HIB and pneumovax before elective adrenalectomy

### Microanatomy

See John Laycock's lecture for structure of adrenal gland





All hormones have Steroid precursor.

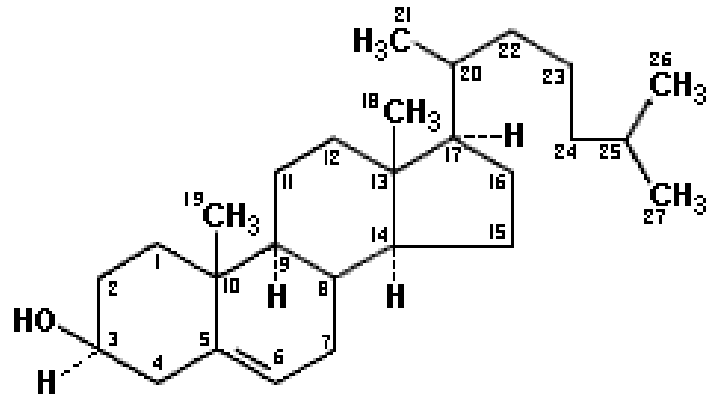
## Hormones

Blood borne circulating messengers

- **Peptides**
- **Steroids**
- **Amines**

### *Cholesterol*

- 27 carbon compound
- Basic cyclic structure 17C
- Side chain 8C
- Pregnenolone - Most basic steroid hormone, as just involves removal of part of the cholesterol side chain
- Pregnenolone can then be oxidised, hydroxylated etc to form mineralocorticoids (e.g. aldosterone) and glucocorticoids (e.g. cortisol) – the difference between aldosterone and cortisol is just position of OH group
- The side chain can be removed completely and then changed to form testosterone
- Disorders come from excess/absence/abnormal function of enzymes within the hormone synthesis pathways



### *Synthesis pathways*

#### **Cholesterol**

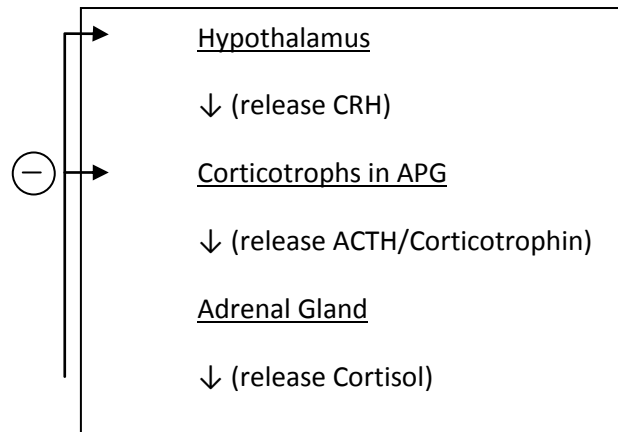
↓

<b>Progesterone</b>	→	<b>17 OH Progesterone</b>	→	<b>Sex steroids</b>
↓ (21)		↓ (21)		↓
<b>11 Deoxycorticosterone</b>		<b>11 Deoxycorticosterone</b>		<b>(Androgens)</b>
↓ (11)		↓ (11)		↓
<b>Corticosterone</b>		<b>Cortisol</b>		<b>(Oestrogens)</b>
↓ (18)		(GLUCOCORTICOID)		

#### **Aldosterone**

(MINERALOCORTICOID)

Note: Number indicates carbon which is oxidised.

Hypothalamo Pituitary Adrenal Axis

- Hormones regulate hormones
- **POMC (Pro-opio-melanocortin)**
  - POMC is a large precursor protein that is cleaved to form a number of smaller peptides, including ACTH, MSH and endorphins
  - An increase in MSH leads to darkened skin, therefore people who have pathologically high levels of ACTH may become tanned

Addison's Disease

- Primary adrenal failure
- Autoimmune disease where the immune system wipes out the adrenal cortex
  - Autoimmune VITILIGO – antibodies against the skin cause patches of depigmentation
- Most common cause is tuberculosis of the adrenal glands
- No cortisol or aldosterone, therefore increased POMC leading to increased ACTH and MSH leading to increased pigmentation of the skin
- The lack of cortisol and aldosterone leads to salt loss, reduces the blood pressure, therefore death from hypotension may occur

Urgent treatment of Addisonian crisis

- Rehydrate with normal saline
- Give dextrose to prevent hypoglycaemia which could be due to the glucocorticoid deficiency
- Give cortisol replacement – HYDROCORTISONE or other glucocorticoid

Cushing's SyndromeBiological actions of excess cortisol

- Impaired glucose tolerance (diabetes)
- weight gain (increase fat, lose protein), with fat redistribution – centripetal obesity
- thin skin and easy bruising, poor wound healing
- hirsutism (facial hair) and acne
- striae (stretch marks)
- proximal myopathy (muscle weakness)
- mental changes (depression)

- osteoporosis
- Hypertension
- moon face – fat deposition in cheeks
- buffalo hump (interscapular fat pad)

### *Causes*

Excess cortisol or other glucocorticoid:

- Taking steroids by mouth (common)
- pituitary dependent Cushing's disease (pituitary adenoma)
- Ectopic ACTH (lung cancer – glucocorticoid released from wrong location in body, i.e. the lungs)
- adrenal adenoma or carcinoma

### *Clinical signs on examination*

- Thin skin
- proximal myopathy
- centripetal obesity
- diabetes, hypertension and osteoporosis
- immunosuppression (reactivation of TB)
- moon face

### *Syndrome vs. Disease*

- **Cushing's syndrome** – where the cause is unknown, but clinical features observed
- **Cushing's disease** – where cause is determined to be PITUITARY ADENOMA

### *Steroid Side effects*

- Hypertension
- Diabetes
- Osteoporosis
- Immunosuppression
- Easy bruising
- Poor wound healing, thin skin

NB: side effects are the same as clinical signs of Cushing's syndrome

### Aldosterone producing Adenoma

- In adrenal glands- Known as CONN'S syndrome
- Hypertension
- Oedema
- Low potassium

# Tutorial 5: Adrenal Disorders

Endo 9 - Professor K Meeran ([k.meeran@imperial.ac.uk](mailto:k.meeran@imperial.ac.uk))

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## Case History

### Case 1

A 30 year old man suffers from adrenal failure.

### Questions:

- 1. What symptoms will he complain of? Briefly explain why he has such a good tan, despite not going on a sunny holiday.**
  - Symptoms
    - Postural hypotension – low blood pressure, will feel dizzy which may cause him to collapse or faint
    - Weight loss
    - Increased pigmentation with autoimmune vitiligo seen
  - Explanation
    - He will have insufficient cortisol and aldosterone production from the adrenal glands
    - This will lead to increased ACTH and hence MSH levels in the blood in order to try and increase the cortisol production
      - MSH causes increased pigmentation of the skin, giving a tanned appearance

### Case 2

A 55-year old female complains that she has been increasing in weight over the past five years. She also has a five-year history of high blood pressure.

### Questions:

- 1. What are the most likely hormonal causes of this high blood pressure?**
  - Increased salt concentration in the blood, which is due to either increased cortisol, aldosterone or adrenaline production
  - Conn's syndrome: excess aldosterone production – could be due to tumour in the zona glomerulosa
  - Cushing's syndrome: excess cortisol production - could be due to tumour in zona fasciculata or the anterior pituitary gland
  - Pheochromocytoma: excess adrenaline production
  - Oral steroid intake
- 2. A year ago, she fell over and fractured her hip. A bone density scan revealed that she had osteoporosis. What is osteoporosis?**
  - Osteoporosis: decreased bone mass and decreased bone density, leading to an increased risk of fractures
  - It is associated with increased osteoclast activity and decreased osteoblast activity
    - Osteoclasts: break down bone
    - Osteoblasts: build up bone
  - Associated with low oestrogen/testosterone, therefore common in post-menopausal women
- 3. Three months ago, she developed polyuria and polydipsia. She saw her general practitioner who noted that she had glycosuria on dipstick testing. What important tests should be performed?**

Blood glucose levels at fasting.

4. **Over the last few weeks, she has had progressive weakness, affecting her thighs, with difficulty climbing stairs. What is this condition called?**

Proximal myopathy: this occurs due to stimulation of proteolysis and suppression of protein synthesis due to excess cortisol

5. **On direct questioning she notes that the shape of her face has changed. She also mentions that she bruises easily, and that a wound on her shin that she had six months ago has not healed. What clinical signs would you expect to find on examination?**

- Weight gain
- Fat redistribution: centripetal obesity; moon face; buffalo hump
- Proximal myopathy
- Diabetes, hypertension and osteoporosis
- Thin skin, associated with poor wound healing
- Striae

6. **On the basis of your overall interpretation, what is the likely diagnosis?**

Cushing's syndrome

## The Gonads I

Endo 10 - Dr Pat Cover ([p.cover@imperial.ac.uk](mailto:p.cover@imperial.ac.uk))

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1. **Describe the stages of gametogenesis and the process of steroidogenesis in male and female gonads.**
2. **Label diagrams illustrating the principal structures of the testes and ovaries.**
3. **Draw simple flow charts illustrating the synthesis of progesterone, 17 $\beta$ -oestradiol and testosterone.**
4. **Describe the principal ovarian and endometrial changes that occur during the menstrual cycle.**
5. **Relate the synthesis of the major gonadal steroids in males and females to the relevant hormones of the hypothalamo-adenohypophysial axis.**
6. **Describe how the cyclic production of ovarian steroids is linked to the endometrial, cervical and other changes of the menstrual cycle.**
7. **Describe the actions of the gonadal steroids in males and females.**
8. **Identify the principal features of the control systems operating on the production of the gonadal steroids, with particular reference to negative and positive feedback loops, in males and females.**
9. **Define the terms primary and secondary amenorrhoea.**
10. **List the principal causes of infertility with particular references to endocrine causes.**
11. **Name the two major functions of the testes and, with the use of a simple diagram, describe how they are regulated by the hypothalamo-pituitary axis.**
12. **With the use of simple diagrams that distinguish between the follicular (early, mid, late) and luteal phases of the menstrual cycle, summarise the endocrine regulation of ovarian function.**

### Introduction

- In females – the gonads develop as the ovaries
- In males – they develop as the testes (SRY gene directs this differentiations)

2 functions:

- **Gametogenesis:** production of gametes for reproduction
  - In males – spermatogenesis
  - In females – oogenesis
- **Steroidogenesis:** production of steroid hormones
  - In males – androgens (also oestrogens and progestogens)
  - In females – oestrogens and progestogens (also androgens)

### Gametogenesis

- Derived from germ cells, which multiply and increase in number before birth
- In males, SPERMATOGONIA levels remain relatively constant through life (6-7million)
- In females, OOGONIA reach 5-6million by 24 weeks of gestations, but then no more are produced
  - These then enter the first stage of meiosis where development is halted until puberty
  - Rapid ATRESIA of oogonia occurs before birth, therefore at birth numbers have reduced to 2million
  - By puberty, < half remain, and by menopause number of oogonia virtually 0
  - Only 3-4 hundred ever reach ovulation

### *Spermatogenesis*

- Begins at puberty
- Some primary spermatocytes continually return to QUIESCENT STAGE (spermatogonia stage) – therefore a pool of spermatogonia remains available for subsequent cycles throughout life
  - Therefore retain some spermatogenic capability throughout life, producing 300-600 sperm/gm testis/second

### *Oogenesis*

- Initial number of oogonia in fetus is approx 6 million – exist in PRIMORDIAL FOLLICLES
- Primary oocytes halted at prophase during first meiotic division
- Then primordial follicles enter process of ATRESIA - By birth the total number of oogonia is approximately 2 million, and by puberty < 0.5 million
- Only at puberty under influence of FSH does the first meiotic division finish and the cycle continues
- The last step of the cycle occurs at fertilisation

**Germ Cell** (44 + XY – diploid)

↓

**Spermatogonia** (44 + XY – diploid)

↓ (Mitotic division)

**Primary Spermatocytes** (44 + XY – diploid)

↓ (First meiotic division)

**Secondary Spermatocytes** (22X or 22Y – haploid)

↓ (Second meiotic division)

**Spermatids** (22X or 22Y – haploid)

↓

**Spermatozoa** (22X or 22Y – haploid)

**Germ Cell** (44 + XY – diploid)

↓

**Oogonia** (44 + XY – diploid)

↓ (Mitotic division)

**Primary Oocytes** (44 + XY – diploid)

↓ (First meiotic division)

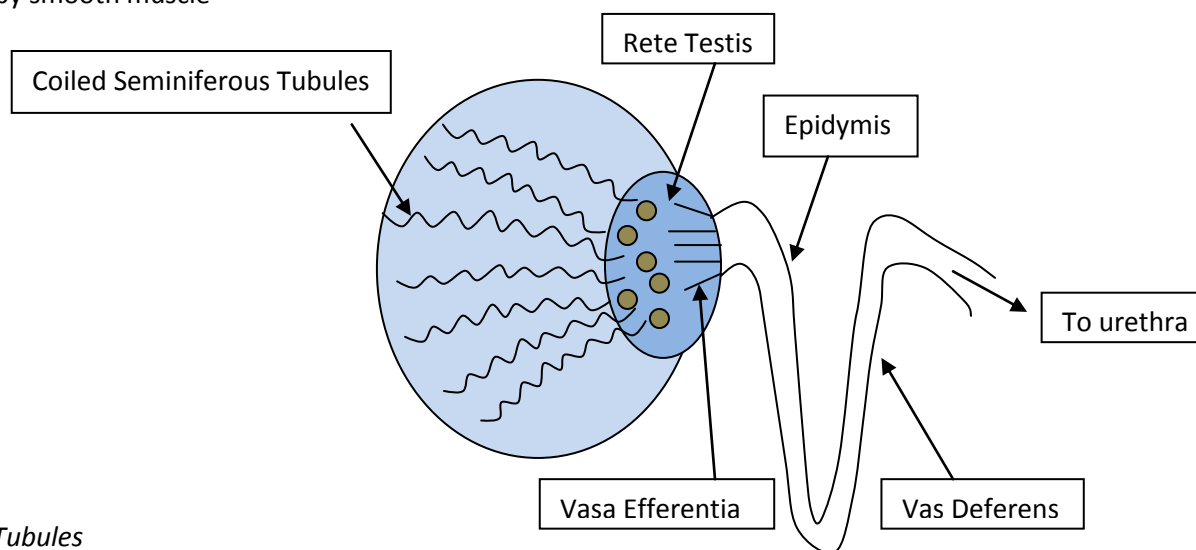
**Secondary Oocytes** + first polar body (both 22X– haploid)

↓ (Second meiotic division)

**Ovum** + second polar body (both 22X– haploid)

## The Testes

- Spermatogenesis occurs in the coiled seminiferous tubules
- Spermatozoa are eventually released into the lumen of the tubules, where they migrate to the rete testis via collecting ducts
- The spermatozoa are then drained from the rete testis via the vasa efferentia into the epidymis
- They then mature in the epidymis, and are propelled to the urethra by the vas deferens which is surrounded by smooth muscle



### *Coiled Seminiferous Tubules*

- Consists of a lumen surrounded by SERTOLI CELLS connected by tight junctions in the periphery
- Spermatogonia are engulfed into the sertoli cell, where they develop in the cytoplasm into primary and secondary spermatocytes and are released into the lumen of the tubule as spermatozoa
- outside the seminiferous tubule are LEYDIG CELL clusters, which are the site of testosterone production

### *Testicular Cells*

#### ➤ **Sertoli cells**

- Form the seminiferous tubules
- Synthesis FSH and androgen receptors
- In response to FHS produce INHIBIN
- Intimately associated with developing spermatocytes etc

#### ➤ **Leydig cells**

- Lie outside the seminiferous tubules
- Synthesis LH receptors
- In response to LH are principal source of testicular androgens (mainly TESTOSTERONE)

## The Ovaries

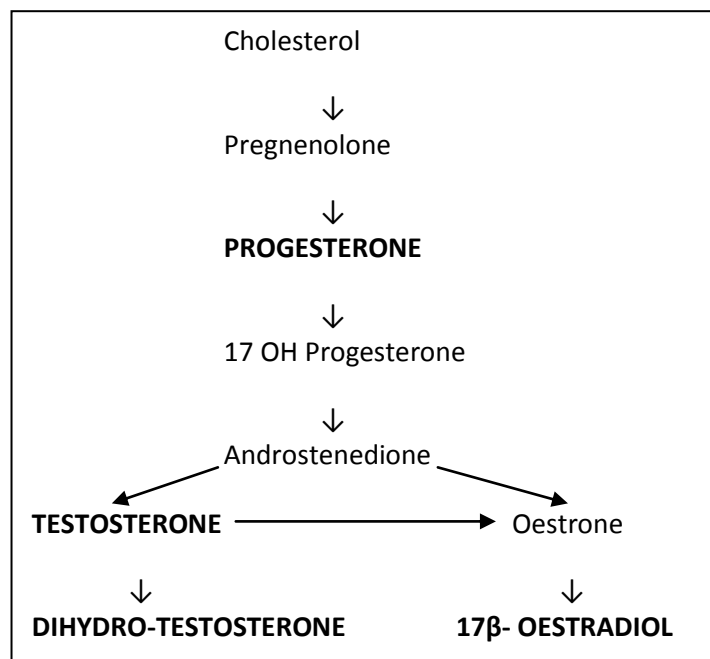
- The ovarian stroma consists of:
  - Primordial follicles undergoing atresia
  - GRAFFIAN FOLLICLE (just before ovulation)
  - Remnants of corpus luteum (after ovulation)
- A graffian follicle consists of an ovum surrounded by follicular fluid
  - A layer of GRANULOSA cells followed by a layer of THECAL cells surround the fluid at the periphery of the follicle

## Steroidogenesis

- From precursor cholesterol
- Products depend on enzymes – only the adrenals have the necessary enzymes for aldosterone and cortisol synthesis
- The Gonads synthesis:
  - Progestogens (C21)
  - Androgens (C19)
  - Oestrogens (C18)

## The Menstrual Cycle

- Approx 28 days (20-35+)
- Begins on 1<sup>st</sup> day menstruation
- Ovulation occurs at day 14
- Consists of:
  - Ovarian Cycle – follicular phase, ovulation & luteal phase
  - Endometrial Cycle – proliferative phase & secretory phase
- The endometrium consists of an epithelium and stromal layer
  - Changes are due to hormone changes in the ovarian cycle
- The Follicular phase of the ovarian cycle – oestrogen (17 $\beta$ - OESTRADIOL) production – stimulates proliferative phase of endometrial cycle
- The luteal phase of the ovarian cycle – progesterone and 17 $\beta$ - Oestradiol production – stimulates secretory phase of endometrial cycle



## *The ovarian cycle*

- **PRE-ANTRAL follicle**
  - Developed in the absence of hormones
  - Ovum surrounded by layer of cells
- **EARLY ANTRAL follicle**
  - Ovum surrounded by GRANULOSA cells and THECAL cells
  - Follicle present – ANTRAL filled space
- **LATE ANTRAL follicle**
  - Same as early antral follicle
  - Follicle increases in size, therefore more antral filled space surrounding ovum



- **GRAFFIAN follicle**
- **OVULATION**
- Ovum released
- Cells form CORPUS LUTEUM

*Hormone Production during ovarian cycle*

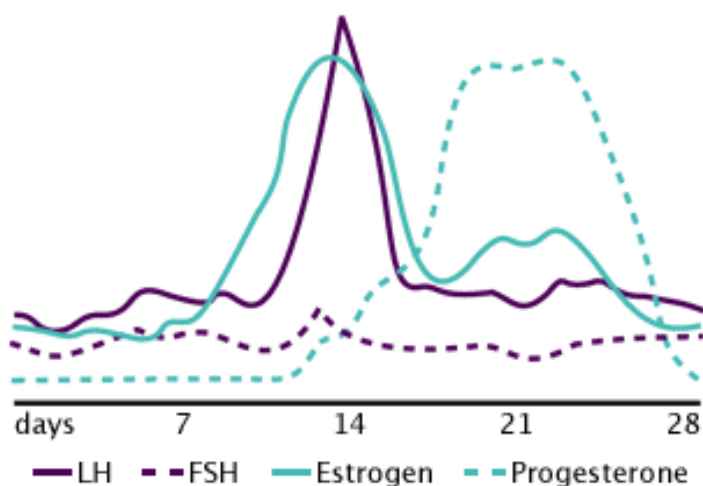
- Follicle influenced by FSH and LH
- Thecal cells produce ANDROGENS
- Androgens stimulate the granulosa cells (which contain AROMATASE) to produce 17β- OESTRADIOL
- After ovulation, the corpus luteum converts androgens → 17β- Oestradiol

*Endometrial Cycle*

Day of Cycle	Event	Dominant Hormone Influence	Endometrium Changes	Gland Changes
6-14	Proliferative Phase	Oestrogen	EARLY PHASE: Thin endometrium	EARLY PHASE: Straight glands
			LATE PHASE: Thickens and moistens	LATE PHASE: Glands enlarge, coil and have increased blood supply
14-15	Ovulation			
15-28	Secretory Phase	Progesterone (plus oestrogen)	Becomes secretory	Secrete glycogen, mucopolysaccharides etc Mucosa become engorged with blood
1-5	Menstruation		Becomes necrotic and is shed	

*Summary*

- LH and FSH peak at ovulation
- Oestrogen peaks just before ovulation, then troughs then is produced by the corpus luteum so increases again
  - Falls dramatically again before menstruation
- Progesterone is limited to the luteal phase
- Oestrogen and progesterone exert **NEGATIVE** feedback at the hypothalamus and anterior pituitary gland for **GONADOTROPHIN** release
- If fertilisation does not occur, oestrogen falls and menstruation occurs
- **BASAL BODY TEMP:** increases at ovulation, indicator that ovulation is taking place
  - Attributed to the action of progesterone



# The Gonads II

Endo 11 - Professor John Laycock ([j.laycock@imperial.ac.uk](mailto:j.laycock@imperial.ac.uk))

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## Testosterone

- First androgen produced is ANDROSTENEDIONE, which is then converted to TESTOSTERONE
- Testosterone binds to the androgen receptor, and is the precursor to the more powerful androgen DIHYDROXYTESTOSTERONE (DHT)
  - Reduction involving 5-ALPHA-REDUCTASE
  - DHT has an increased affinity for the androgen receptor
- Testosterone can also undergo AROMITIZATION by AROMATASE enzyme to form OESTRONE and then 17-BETA-OESTRADIOL (which is the main circulating oestrogen)
  - Oestrogens also are important in the development of behaviour in males, and is therefore produced in the SERTOLI cells of the testes as well as the ovaries in women
- Testosterone and DHT are produced in:
  - Prostate
  - Seminiferous tubules (in testis)
  - Seminal vesicles
  - Skin
  - Brain
  - Anterior pituitary gland (adenohypophysis)
- 17-beta-oestradiol is produced in:
  - Adrenals
  - Sertoli cells (testis)
  - Liver
  - Skin
  - Brain

## *Transport of testosterone and DHT*

- **In blood** – bound to plasma proteins as the androgens are LIPOPHILIC therefore need to be bound to prevent excess effects
  - SEX HORMONE BINDING GLOBULIN (SHBG) – 60% bound
    - Specific for androgens and oestrogens
  - Albumin – 38% bound
  - Free bioactive component – 2%
- **In seminiferous fluid**
  - Bound to ANDROGEN BINDING GLOBULIN

## *Principle actions*

- **In fetus**
  - Development of male internal and external genitalia
  - General growth (acting with other hormones, stimulates e.g. protein anabolism)
  - Behavioural effects during development
- **In adults**
  - Spermatogenesis

- Growth and development of:
  - Male genitalia
  - Secondary accessory sex glands e.g. prostate, seminal vesicles etc
  - Secondary sex characteristics e.g. receding hairline, facial hair, bulk, narrow hips
- Protein anabolism
- Pubertal growth spurt (along with growth hormone)
- Feedback regulation
- Behavioural effects (CNS) e.g. aggression, competitiveness

### Oestrogens

- *Definition: any substance (natural or synthetic) which induces mitosis in the endometrium*
- Examples
  - 17 $\beta$ -oestradiol (main one during menstrual cycle; most potent)
  - Oestrone (precursor)
  - Oestriol (main oestrogen produced in pregnancy)

#### *Principal actions*

- Final maturation of follicle during follicular phase of menstrual cycle
- Induces LH surge resulting in ovulation
- Stimulates growth and proliferation (mitosis) of the endometrium
- Effects of vagina, cervix e.g. development of glands
- Stimulates growth of ductile system of breast
- Decreases sebaceous gland secretion, which may be associated with acne
- Increases salt (and water) reabsorption
- Increases plasma protein synthesis (hepatic effect)
- Metabolic actions e.g. changing lipid profiles by stimulating HDL as opposed to LDL (possible protection for CVD)
- Stimulates osteoblasts – lost after menopause, can have protective effect against osteoporosis
- Influences release of other hormones (e.g. prolactin, thyrotrophin)
- Feedback regulation
- Behavioural influences

NB: see protective effects on cardiovascular system and against osteoporosis

### Progestogens

- Definition: any substance (natural or synthetic) which induces secretory changes in the endometrium
- Examples:
  - Progesterone
  - 17-alpha-hydroxyprogesterone

#### *Principal actions*

- Stimulates secretory activity in the endometrium and cervix
- Stimulates growth of alveolar system of breast
- Decreases renal NaCl reabsorption (competitive inhibition of the aldosterone)
- Associated with increases in basal body temperature

- This is a useful marker of ovulation, as it results in a 0.1-0.2 degree increase

### Steroid Mechanism of Action

- Steroid hormones are LIPOPHILIC therefore pass through cell membranes
  - This means they must bind with INTRACELLULAR RECEPTORS
- Hormone-receptor complex acts as a TRANSDUCTION MOLECULE, binding with DNA to stimulate transcription etc
- Have important genomic effects, but these are not seen instantly as takes time to make new proteins etc
- Non-genomic effects are also possible

### Hypothalamo-Pituitary-Gonadal Feedback Loops

#### *The Hypothalamo-Pituitary-Testicular Axis*

- **Hypothalamus**
  - GONADOTROPHIN RELEASING HORMONE (GnRH) released in PULSITILE patterns
- **Anterior pituitary Gland**
  - Gonadotrophs release GONADOTROPHINS: LH & FSH
  - Enter general circulation
- **Testis**
  - LH (in LEYDIG cell); stimulates TESTOSTERONE production – stimulates:
    - VIRILISATION
    - SPERMATOGENESIS
  - FSH (in SEROLI cell); stimulates INHIBIN production
    - Also stimulates SPERMATOGENESIS
- NB: with regards to spermatogenesis – testosterone is insufficient on its own to start cycle, but in conjunction with FSH is important in the maintenance of the spermatogenesis cycle

### **FEEDBACK**

- Testosterone:
  - DIRECT inhibition of FSH and LH release from the anterior pituitary gland
  - INDIRECT inhibition of the pulse generator releasing GnRH from the hypothalamus, which in turn also reduced gonadotrophin (FSH & LH) release
- Inhibin:
  - Same effects as testosterone

### **SUMMARY – Endocrine control of testicular function**

- **Androgen production**
  - stimulated by GnRH/LH system
  - reduced by testosterone
    - direct negative feedback to reduce LH release from anterior pituitary gland
    - indirect negative feedback to slow hypothalamic GnRH pulse generator
- **Spermatogenesis**
  - stimulated by GnRH/FSH system
  - also requires **GnRH/LH/testosterone** system for complete spermatogenesis
  - limited by inhibin negative feedback (direct and indirect)

### *The Hypothalamo-Pituitary-Ovarian Axis*

- Same as testicular axis, except FSH and LH act on the OVARIES
- Must consider the effects of each hormone during the different phases of the menstrual cycle:
  - Early follicular
  - Early-mid follicular
  - Mid follicular
  - Late follicular
  - Luteal

#### **EARLY FOLLICULAR PHASE**

- At the end of the previous menstrual cycle, there is a decreasing oestrogen and progesterone production, but the steroid hormones still result in an INHIBITION of FSH and LH
  - This is due to direct negative feedback on the anterior pituitary gland
  - Indirect negative feedback on the hypothalamus

#### **EARLY-MID FOLLICULAR PHASE**

- The decrease in steroid hormones (oestrogen and progesterone) from the previous cycle reduces inhibition of gonadotrophins from the anterior pituitary, therefore LH and FSH are released
- LH acts on THECAL cells within the ovaries (binding to the LH receptor), inducing androgen synthesis
  - Androgens are then released into the general circulation, follicular fluid, or taken up by GRANULOSA cells within the ovary
- FSH binds to FSH receptor on GRANULOSA cells, inducing the AROMATISATION of androgens to 17-beta-oestradiol
  - This is known as a local positive feedback loop which enhances oestradiol production in developing follicles – CRYPTOCRINE EFFECT

#### **MID-FOLLICULAR PHASE**

- The steps of the early-mid follicular phase continues, leading to an exponential increase of oestradiol, which exerts a negative feedback effect resulting in decreased FSH and LH production
  - There is also a production of INHIBIN from the follicle
  - *Selective* negative feedback loop by oestrogen and inhibin on the GnRH-FSH system results in ATRESIA (regression) of all follicles that are still FSH dependent
- GRAFFIAN FOLLICLE
  - largest follicle no longer requires FSH to develop and proliferate
  - It keeps growing and producing large amounts of 17b-oestradiol

#### **LATE FOLLICULAR PHASE**

- This rising concentration of 17b-oestradiol, in the absence of progesterone, for a minimum of 36h and at a certain level results in the positive feedback switch on the hypothalamo-adenohypophysial system
- This triggers the LH SURGE (as well as a lesser FSH surge) which stimulates the final development of ovum and OVULATION
  - There is also a surge in 17-ALPHA-HYDROXY-PROGESTRONE just before this surge, which could be responsible for the final increase in oestrogen concentration

**LUTEAL PHASE**

- After the gonadotrophin surges, there is an increase in the production of steroids 17-BETA-OESTRADIOL and PROESTERONE
  - If fertilization does not occur, progesterone, oestradiol and inhibin exert a negative feedback on LH and FSH release, leading to LUTEOLYSIS and MENSTRUATION
- The steroid concentrations then start to decrease towards the end of the cycle

Clinical Correlates*Amenorrhoea*

- Definition: absence of menstrual cycles
- Primary – never had periods
- Secondary – did happen but have stopped
- OLIGOMENORRHOEA – infrequent cycles
  - Causes: various
    - Absence of LH surge e.g. due to insufficient oestrogenic effect at the end of follicular phase etc

*Infertility*

- Means unable to get pregnant
  - Men – unable to IMPREGNATE
- Various causes:
  - Physical
  - Psychological
  - Emotional
  - Endocrine problems
- Excess prolactin (e.g. from a PROLACTINOMA) can be a cause of infertility

## The parathyroids and the endocrine control of calcium metabolism

Endo 12 - Professor John Laycock ([j.laycock@imperial.ac.uk](mailto:j.laycock@imperial.ac.uk))

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1. List the functions of calcium in the body.
2. Identify the principal organs involved in calcium metabolism.
3. Identify the bone cells and their functions.
4. List the principal hormones which regulate blood calcium ion concentration, and their sites of synthesis.
5. Briefly describe how parathormone, 1,25-dihydroxycholecalciferol (calcitriol) and calcitonin are synthesized.
6. Describe the principal effects of parathormone, 1,25-dihydroxycholecalciferol and calcitonin on bone, the kidneys and the intestinal tract.
7. Describe the mechanisms of action of parathormone, 1,25-dihydroxycholecalciferol and calcitonin.
8. Explain how parathormone, 1,25-dihydroxycholecalciferol and calcitonin production are controlled, identifying the principal stimulus in each case.
9. List the principal causes of hypocalcaemia.
10. List the principal causes of hypercalcaemia.

## 11. Distinguish between primary, secondary and tertiary hyperparathyroidism.

### Calcium

- Most calcium is present in the body as calcium salts
- It is mainly found in bone (99%, approx. 1kg) as complex hydrated calcium salt (HYDROXYAPATITE crystals)
- In blood, some is present as ionized calcium ( $\text{Ca}^{2+}$ ), some bound to protein and the tiny bit left as soluble salts
- Only the free (unbound)  $\text{Ca}^{2+}$  is bioactive

### *Roles*

- Maintenance of neuromuscular excitability
- Muscle contraction
- Strength in bones
- Intracellular second messenger
- Intracellular co-enzyme activity
- Hormone/neurotransmitter stimulus-secretion coupling
- Blood coagulation (factor IV)

### *Handling by the body*

- Intake via diet (approx 100 mg/24hr)
- Then absorbed via GI tract into the blood
  - Some is lost from the blood into the GI tract via and excreted as faeces (approx 850 mg/24hrs)
- From the blood, there are two target tissues:
  - Kidneys – small calcium ions enter the kidney nephrons where final regulation of ion concentrations occur and excess is excreted via the urine (approx 150 mg/25hr)
  - Bone (and all cells) – taken up from the blood, but calcium is also broken down and re-released into the bloodstream
  - There is also INVISIBLE loss of calcium via dead cells, hair, nails etc

### *In the blood*

- The total concentration of calcium in the blood is approx 2.5mM
- This is controlled very precisely, as many metabolic processes within the body are Calcium mediated
- 50% of calcium remained UNBOUND – this is the ionized component which is biologically active
- 45% is bound to PLASMA PROTEINS (approx 1.13Mm)
- 5% remain as DIFFUSIBLE SALTS (approx 0.13 Mm) – these include citrate and lactate are can readily diffuse through cell membranes

### *Ion regulation*

- Concentration is INCREASED by:
  - PARATHYROID HORMONE (PTH) – a polypeptide hormone
  - 1, 25 (OH)<sub>2</sub> VITAMIN D<sub>3</sub> metabolite – DIHYDROXYCHOLECALCIFEROL, or CALCITROL – a steroid hormone
- Concentration is DECREASED by:

- CALCITONIN – a polypeptide hormone with a physiological role that is not completely understood, but is relatively short lasting and increases in levels during pregnancy
- PTH is released by PARATHYROID GLANDS
- Calcitonin is released by PARAFOLLICULAR CELLS

### PTH

- Initially synthesised as protein PRE-PRO-PTH
- 84 amino acids long
- Binds to transmembrane G-protein linked receptors
  - Activated ADENYL CYCLASE, but also probably phospholipase C as a second messenger

### Hormone Actions

#### ➤ **KIDNEYS**

- Increased Ca<sup>2+</sup> reabsorption from tubular fluid in the proximal and distal tubules
- Increased PO<sub>4</sub><sup>3-</sup> excretion in urine
- Stimulates 1α hydroxylase activity
  - This hydroxylates 25 OH Vit D<sub>3</sub> → 1,25 (OH)<sub>2</sub>D<sub>3</sub>
  - The 1,25 (OH)<sub>2</sub>D<sub>3</sub> then acts on the small intestine
- SMALL INTESTINE
  - The 1,25 (OH)<sub>2</sub>D<sub>3</sub> acts to:
    - Increase Ca<sup>2+</sup> absorption into the blood
    - Increase absorption of PO<sub>4</sub><sup>3-</sup>
- these both lead to an influence in the blood calcium concentrations

#### ➤ **BONES**

- Stimulate OSTEOCLASTS (breakdown)
- Inhibit OSTEOBLASTS (rebuilding)
- This leads to increased bone reabsorption

### *Effect on Blood*

- Increased Ca<sup>2+</sup> reabsorption and increased PO<sub>4</sub><sup>3-</sup> excretion from the kidneys leads to increased Ca<sup>2+</sup> concentration in blood
- Increased Ca<sup>2+</sup> and PO<sub>4</sub><sup>3-</sup> absorption from the small intestine leads to increased blood Ca<sup>2+</sup>
- Increased Ca<sup>2+</sup> MOBILIZATION due to increased osteoclast activity → increased blood Ca<sup>2+</sup>

### *Action in Bone*

- PTH leads to the inhibition of new bone formation
  - It binds with the PTH receptor on osteoblasts, which stimulate OSTEOCLAST STIMULATING FACTOR (OAFs, e.g. cytokines)
- OAFs stimulate osteoclasts to increase bone matrix breakdown and release Ca<sup>2+</sup> and PO<sub>4</sub><sup>3-</sup> → increased bone reabsorption
- NOTE: PTH does not have a direct effect on osteoclasts as there are no receptors present

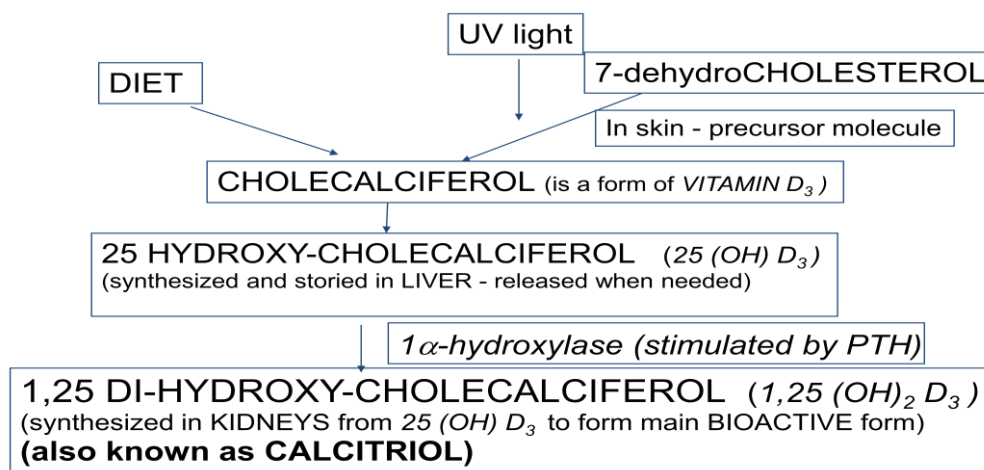


### *PTH Regulation*

- Decreased plasma  $\text{Ca}^{2+}$  →
  - Increased PTH production in parathyroid glands
  - This leads to increased  $\text{Ca}^{2+}$
- The increased  $\text{Ca}^{2+}$  then exhibits **NEGATIVE FEEDBACK** on the parathyroid glands
- Increased PTH →
  - Synthesis of  $1,25(\text{OH})_2\text{D}_3$
  - Synthesis exerts +ve influence increasing plasma  $\text{Ca}^{2+}$ , but a **NEGATIVE** influence on the parathyroid glands to reduce PTH production, which then has a secondary effect reducing  $\text{Ca}^{2+}$
- Catecholamines have a positive effect on the parathyroid glands via beta receptors

### Dihydroxy-cholecalciferol

#### *Synthesis*



#### *1, 25 (OH)<sub>2</sub> D<sub>3</sub> Actions*

- **On the small intestine**
  - Increased  $\text{Ca}^{2+}$  absorption
  - Increased  $\text{PO}_4^{3-}$  absorption
- **On bone**
  - Increased osteoblast activity
    - Therefore increased storage of  $\text{Ca}^{2+}$  in the bone
- **On the kidneys**
  - Increased  $\text{Ca}^{2+}$  and  $\text{PO}_4^{3-}$  reabsorption in the proximal tubule

### Calcitonin

- Synthesized as **PRE-PROCALCITONIN**
- Calcitonin is 32 amino acid long polypeptide
- Binds to transmembrane G-protein linked receptor which leads to the activation of adenylyl cyclase or PLC as second messenger systems

#### *Actions and regulation*

- Stimulus: increased plasma  $\text{Ca}^{2+}$  concentration stimulates the parafollicular cells of the thyroid to produce calcitonin
  - GASTRIN also stimulates this
- Calcitonin action on bone – inhibition of osteoclast activity which decreases the plasma concentration
- Calcitonin action on the kidneys – increased urinary excretion of  $\text{Ca}^{2+}$  (as well  $\text{Na}^{+}$  and  $\text{PO}_4^{3-}$ ) which again decreases the plasma concentration

## Clinical Correlates

### *Hypoglycaemia*

- Endocrine causes:
  - **HYPOPARATHYROIDISM**
    - Decreased Plasma [ $\text{Ca}^{2+}$ ]
    - Increased Plasma  $\text{PO}_4^{3-}$
    - Reduced PTH
  - **PSEUDOHYPOPARATHYROIDISM**
    - Decreased Plasma [ $\text{Ca}^{2+}$ ]
    - Increased Plasma  $\text{PO}_4^{3-}$
    - Increased PTH
  - **VITAMIN D DEFICIENCY**
    - Decreased Plasma [ $\text{Ca}^{2+}$ ]
    - Decreased Plasma  $\text{PO}_4^{3-}$
    - Increased PTH
- TETANY – where smooth muscle goes into auto-contraction
  - Can be used to observe where decreases in  $\text{Ca}^{2+}$  have occurred
  - TROUSSEAU’S sign – tetany in the hands can be induced by decreased  $\text{Ca}^{2+}$
  - CHVOSTEK’S sign – the facial nerve can be “tapped” to induce a twitch
- HYPOPARATHYROIDISM
  - consequence of thyroid surgery
  - idiopathic – cause unknown
  - hypomagnesaemia (very rare)
  - suppression by raised plasma calcium concentration (chronic raised  $\text{Ca}^{2+}$  levels inhibit the parafollicular cells)
- PSEUDOHYPOPARATHYROIDISM – also known as Albright hereditary osteodystrophy
  - Due to target organ resistance to PTH (multiple underlying causes; believed to be due to defective G protein)
  - Features include:
    - particular physical appearance (short stature, round face)
    - low IQ
    - subcutaneous calcification and various bone abnormalities (e.g. shortening of metacarpals)
    - associated endocrine disorders (e.g. hypothyroidism, hypogonadism).
- VITAMIN D DEFICIENCY
  - **Rickets** in children
  - **Osteomalacia** in adults

- Clinical feature is the decreased calcification of bone matrix resulting in softening of bone → bowing of bones in children and fractures in adults

### *Hyperparathyroidism*

- Endocrine causes:
  - **PRIMARY HYPERPARATHYROIDISM**
  - **TERTIARY HYPERPARATHYROIDISM**
  - **VITAMIN D TOXICOSIS**
- Note: secondary hyperparathyroidism is NOT associated with hypercalcaemia, but with low or normal plasma calcium levels
- Causes:
  - ADENOMA – within the parathyroids leads to an increase in PTH, which increases the [Ca<sup>2+</sup>]. However there is no response to negative feedback seen.
    - This is PRIMARY hyperthyroidism – results in clubbing of the fingers, and marked periosteal bone erosion in the terminal phalanges
  - LOW PLASMA [Ca<sup>2+</sup>] – e.g. due to renal failure; a decrease in [Ca<sup>2+</sup>] stimulates the parathyroids to produce PTH, which increases the [Ca<sup>2+</sup>] although there is no calcitonin release to counteract this, and there is NO FEEDBACK
    - This is SECONDARY hyperthyroidism
  - INITIAL CHRONIC LOW PLASMA [Ca<sup>2+</sup>] – same as secondary hyperparathyroidism, but as opposed to no feedback, there is no response to the negative feedback
- **Parathormone excess**
  - On the kidneys:
    - Ca reabsorption
    - PO<sub>4</sub> excretion
    - Polyuria
    - Renal stones
    - Nephrocalcinosis
    - 1,25 (OH)<sub>2</sub> D<sub>2</sub> synthesis
  - On the GI tract:
    - Gastric acid
    - Duodenal ulcers
  - On bone:
    - Bone lesions
    - Bone rarefaction
    - Fractures