The Investigations of the Pituitary Gland

Essential for understanding this presentation:

1) **Anatomy:** The Pituitary Gland and its surroundings

2) **Biochemistry:** Hormones produced by the Pituitary Gland

3) **Physiology:** Function of the hormones produced by the Pituitary Gland

First then can one start on a journey to investigate abnormal functions of the Pituitary gland
The Investigations of the Pituitary Gland

Objectives:

1) Describe the mechanisms of endocrine hypofunction and hyperfunction.

2) Differentiate among primary, secondary and tertiary endocrine disorders.

3) Discuss - based on the normal physiology - the rationale behind the investigations of the functions of the Pituitary Gland.
The Investigations of the Pituitary Gland

Essential for understanding the investigations

1) **Anatomy:**

2) **Biochemistry:**

3) **Physiology:**

4) **Diseases**
Essential anatomy

Connections to/from hypothalamus (nerve and vessels) to the pituitary gland

The hypophyseal portal system

From Porth and Matfin Pathophysiology – Concepts of Altered Health states 2009
Location

Neighboring structures:
(the optic chiasm, sinuses, bone-structures, vessels)

Which way would you take to reach the Pituitary Gland for an operation?

Through the nose
Essential anatomy

Visualize it

You need that skill when interpreting images (ultrasound, X-rays, CT- and MRI scans etc.)
The Investigations of the Pituitary Gland

Histology

Three lobes
anterior, intermediate, and posterior
( Neurohypophyphysis, Adenohypophysis )

Basophil: ACTH ‘family’, TSH, FSH, LH and ICSH

Acidophil: GH, STH and PRL

Pictures from http://www.vivo.colostate.edu/hbooks/pathphys/endocrine/hypopit/histo_adeno.html
The Investigations of the Pituitary Gland

Essential for understanding the investigations

1) Anatomy:

2) Biochemistry:

3) Physiology:

4) Diseases
The structure of the hormones:

**Polypeptide:**
ACTH, MSH, GH, PRL, ADH and Oxytocin.

**Glycoprotein:**
TSH, FSH, and LH.
Pro-opiomelanocortin derived peptides

POMC

Biochemical Journal 2010 428, 305-324 - Kathleen G. Mountjoy
Pro-opiomelanocortin derived peptides

POMC

It is split into nine segments, the numbers 126/129 shows the number in the sequence of the amino acids between which the cleavage will take place.

It is a polypeptide build of 241 amino acids.

Note the name: it has something to do with opioids (opio), Melatonin (melano) and corticotropin (cortin).
Pro-opiomelanocortin derived peptides

POMC is the precursor for ACTH and Lipotropin.

Biochemical Journal 2010 428, 305-324 - Kathleen G. Mountjoy
Pro-opiomelanocortin derived peptides

POMC is the precursor for MSH, melanocyte-stimulating hormone (Collectively also known as melanotropin or intermedin)

POMC

Biochemical Journal 2010 428, 305-324 - Kathleen G. Mountjoy
Pro-opiomelanocortin derived peptides

POMC is the precursor for EP, endorphin

CLIP, corticotropin-like intermediate lobe peptide

Biochemical Journal 2010 428, 305-324 - Kathleen G. Mountjoy
Pro-opiomelanocortin derived peptides

POMC

Remember !!

This does not only apply for the pituitary gland

Melanocortin peptides, derived from POMC, are produced in:
1) the ARH (arcuate nucleus of the hypothalamus)
2) neurons and the neurons in the commissural NTS (nucleus of the solitary tract) of the brainstem,
3) in anterior and intermediate lobes of the pituitary,
4) skin and a wide range of peripheral tissues, including reproductive organs.
Pro-opiomelanocortin derived peptides
POMC

The enzymes involved is identified (the colored ovals)

Note thee are several ACTH’s

We will treat them as if there is only ‘one soup’ for now.
Pro-opiomelanocortin derived peptides

POMC

Personal note: This illustrate that we have to realize that working with medicine means constantly learning.

Biochemical Journal 2010 428, 305-324 - Kathleen G. Mountjoy
Pro-opiomelanocortin derived peptides

New Horizon

MC4R activation in the sympathetic nervous system

Skeletal Muscle

Insulin sensitivity

Liver

Triglycerides
Fatty acid oxidation

WAT
Lipolysis

BAT
UCP1
Thermogenesis

Pancreas
Insulin
Pro-opiomelanocortin derived peptides

Central and peripheral regulation of energy homoeostasis mediated through the central melanocortin system
The Investigations of the Pituitary Gland

Essential for understanding the investigations

1) Anatomy:

2) Biochemistry:

3) Physiology:

4) Diseases
If the hormone makes the target organ increase its ‘product’ it **stimulates**

If the product makes the gland decrease its release of hormone it is called **negative feedback**

**General rule:** Negative feedback create simple stable systems
If the product makes the gland increase its release of hormone it is called **positive feedback**

**General rule:** Positive feedback creates unstable systems – Constantly spiraling upward (additional control mechanisms needed)
The Investigations of the Pituitary Gland

If the hormone makes the target organ decrease its ‘product’ it inhibits

That stops the constant upward spiraling positive feedback mechanism – hence inhibitors are important elements in stopping positive feedback.
A new element is added the Controlling Gland

It releases hormones that controls the Gland (releasing hormone)

If the hormone from the gland inhibits the Controlling Gland we have a normal negative feed back system
If the product from the Target Organ also inhibits the controlling gland we have a double negative feedback system:

- Controlling Gland $\rightarrow$ Gland
- Gland $\rightarrow$ Target Organ

Both Short loops

Controlling gland $\rightarrow$ Target Organ is a Long Loop
Physiology

**Tertiary disease**
The cause can be found in the Controlling Gland
Target Organ

**Secondary disease**
The cause can be found in the gland controlling the Target Organ

**Primary disease**
The cause can be found in the Target Organ
## Which hormones are secreted

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<th>Releasing factors</th>
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The Investigations of the Pituitary Gland

Essential for understanding the investigations

1) **Anatomy:**

2) **Biochemistry:**

3) **Physiology:**

4) **Diseases**
Hyper - & Hypo-functions

In principle only two things can go wrong:

Increased production (over production) of hormones: Hyper……dism

Decreased production (under production) of hormones: Hypo……dism

Of cause there can be many underlying causes: Tumor, starvation, infections ……. 
### Hypo - ACTH

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It will be decreased production of glucocorticoids from the adrenal gland.

What will be the result of a decrease ACTH Production in the pituitary gland?
## Hyper - ACTH

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What will be the result of a increased ACTH Production in the pituitary gland?

It will be increased production of glucocorticoids from the adrenal gland.

It should be call secondary adrenal hyperfunction. Traditional it is called *Cushing Disease*.
The gland has a tendency to prioritize its production—Safeguarding the production of the most important at the expense of the least important.

How would prioritize?

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Hormone prioritizing

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**Mnemonic:**  **Go Look For The Adenoma**

Meaning first goes GH then LH ....... Last ATCH

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The Investigations of the Pituitary Gland

Essential for understanding the investigations

1) Anatomy:

2) Biochemistry:

3) Physiology:

4) Diseases

Diagnose
Suppression tests are used mainly for the differential diagnoses of **excessive hormone** secretion.

The substance or an analogue that normally suppress secretion by negative feedback is administered in a sufficient high dose.

The response is measured.

**Failure to suppress** implies that secretion is not under normal feedback control (autonomous secretion).
Simulation tests are used mainly for the differential diagnoses of deficient hormone secretion.

The tropic hormone that normally stimulates secretion is administered in a sufficient high dose.

The response is measured. A normal response exclude and abnormality of the target gland whereas failure to respond confirms it.
Test both trophic and ‘product’

Hormone secretion may very predictable over a 24 hour (circadian) or longer. It may be episodic or may respond predictably to physiological stimuli such as stress.

Simultaneous measurement of both the trophic hormones and their controlling factors, whether hormones or metabolic products, may be more informative than the measurement of either alone.
Test both trophic and ‘product’

An important endocrine principle is that an apparently normal hormone results should be interpreted in the context of the associate hormone axis.

For example, a plasma PTH concentration within the reference range may be abnormal if the plasma calcium concentration is elevated.
Clinical findings of Adrenal insufficiency

Hyperpigmentation:
Skin (bronze tone)
Body creases, nipples,
And mucous membranes

Loss of weight:
Emaciation, anorexia
vomiting, and diarrhea

Hypoglycemia
Poor tolerance to stress,
fatigue
muscle weakness

Cardiac insufficiency,
hypotension

Adrenal atrophy,
destruction

Urinary losses,
sodium, water

Retention of potassium

From Porth and Matfin Pathophysiology – Concepts of Altered Health states 2009
Clinical findings of Adrenal insufficiency

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<td>Orthostatic hypotension</td>
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<tr>
<td>Hyponatremia</td>
<td>Yes 85-90%</td>
<td>Yes 60%</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>Yes 60-65%</td>
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<td>Hyperpigmentation</td>
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From Porth and Matfin Pathophysiology – Concepts of Altered Health states 2009
# Clinical findings of Adrenal insufficiency

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**Why is the symptoms at the top the same in both primary and secondary insufficiency?**

**Why is the symptoms at the bottom different in primary and secondary insufficiency?**

**What would the symptoms be in tertiary insufficiency?**
Clinical findings of Adrenal insufficiency Testing

**Plasma Cortisol**

If plasma Cortisol > 580 nmol/l addison’s adrenal hypofunction unlikely

**Synacthen stimulation test:**

Blood is taken for basal cortisol assay

Synacthen 250 μg IM, Blood at 30 and 60 minutes

Plasma cortisol should increase with at least 200 nmol/l and should reach > 580 nmol/l. Should peak in approximately 30 minutes.

A tetracosactrin (Synacthen®) is a ACTH analog but lacks the antigenic part
Clinical findings of Adrenal insufficiency

Testing

**Plasma ACTH**
Range 10-60 pg/mL
If high indicate Addison disease
If low could be secondary adrenal insufficiency

**CHR stimulation test:**
When the response to the ACTH test is abnormal, a **CRH stimulation test** is helpful in determining the cause of adrenal insufficiency. A synthetic CRH is injected, and the plasma cortisol and ACTH is measured before and after the injection.

High levels of ACTH but little cortisol = Addison.
Low levels of ACTH but little cortisol = secondary adrenal insufficiency is suspected.
Typical clinical findings

A note on nomenclature

**Cushing syndrome** refers to the manifestations of hypercortisolism from **any** cause

**Cushing disease** refers to hypercortisolism from excessive production of ACTH by the pituitary gland

Is Cushing disease a primary / secondary or tertiary disease?
Glucocorticoid Hormone Excess - testing

**Screening:**
Salivary cortisol level

24 hour urine collection analyzed for free cortisol. (5% false-negative rate = if 3 separate collections are normal Cushing's syndrome is most unlikely.

**Suppression test:**
Low-dose overnight dexamethasone suppression test.
1 mg of dexamethasone given at midnight. Blood test for cortisol assay at 8:00 -9:00 the following morning. Failure to suppress to < 50 nmol/l indicates further testing is needed.

From Porth and Matfin Pathophysiology – Concepts of Altered Health states 2009
**Glucocorticoid Hormone Excess - testing**

**48 hours low dose suppression test:**
0.5 mg of low dose dexamethasone orally every 6 hours. Blood test for cortisol assay at 9:00 after 48 hours. Failure to suppress to < 50 nmol/l indicates further testing is needed.
That is Plasma ACTH and plasma CRH is available.

**High Dose Dexamethasone Suppression Test:**
Patients are given 2.0 mg dexamethasone by mouth every 6 hours for 2 days. A 24 hour urine collection for cortisol is performed on the second day of the test. Cortisol suppression suggests a pituitary tumor.
A similar test is performed using a single dose of 8.0 mg at midnight, and a fasting blood draw for cortisol the next morning.

From Crook, Clinical Chemistry and Metabolic Medicine  2006
## Glucocorticoid Hormone Excess - testing

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<th>Test</th>
<th>Pituitary dependent</th>
<th>Ectopic ACTH</th>
<th>Adrenocortical Carcinoma</th>
<th>Adrenocortical Adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma cortisol morning</td>
<td>Raised or normal</td>
<td>Raised</td>
<td>Raised</td>
<td>Raised or normal</td>
</tr>
<tr>
<td>Plasma cortisol evening</td>
<td>Raised</td>
<td>Raised</td>
<td>Raised</td>
<td>Raised</td>
</tr>
<tr>
<td>After low-dose dexamethasone</td>
<td>No suppression</td>
<td>No suppression</td>
<td>No suppression</td>
<td>No suppression</td>
</tr>
<tr>
<td>After high-dose dexamethasone</td>
<td>Suppressed</td>
<td>No suppression</td>
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</tr>
<tr>
<td>Urinary free cortisol</td>
<td>Raised</td>
<td>Raised</td>
<td>Raised</td>
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</tr>
<tr>
<td>Plasma ACTH</td>
<td>Raised or normal</td>
<td>Raised</td>
<td>Low</td>
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</tr>
</tbody>
</table>

From Crook, Clinical Chemistry and Metabolic Medicine  2006
Glucocorticoid Hormone Excess - testing
The ultimate test: Combining imaging and blood test

25-year-old woman with Cushing's disease.

50-year-old man with Cushing's disease.

**Bilateral inferior petrosal sinuses sampling (BIPSS):** this test may be required to separate pituitary from ectopic causes of ACTH-dependent Cushing's syndrome in patients with a normal pituitary gland on brain MRI scan.

Hyperthyroidism

- Fine Hair
- Exophtalmos
- Muscle wasting
- Fine tremor
- Oligomenorrhea
- Pretibial myxedema
- Goiter
- Tachycardia, palpitations, high output failure
- Weight loss

Nervousness
Restlessness
Emotional instability
Insomnia
Sweating, heat intolerance
Increased appetite

From Porth and Matfin Pathophysiology – Concepts of Altered Health states 2009
## Hyperthyroidism

<table>
<thead>
<tr>
<th>Total T4</th>
<th>Total T3</th>
<th>Free T4</th>
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<th>TBG</th>
<th>TSH</th>
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<tbody>
<tr>
<td>Normal</td>
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**Diagnose?**
Hyperthyroidism

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</tr>
<tr>
<td>Hyperthyroid</td>
<td>^</td>
<td>^</td>
<td>^</td>
<td>^</td>
<td>normal</td>
<td>v</td>
</tr>
<tr>
<td>T3 toxis</td>
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<td>^</td>
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<td>^</td>
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<td>^</td>
<td>^</td>
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<td></td>
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<tr>
<td>TBG excess</td>
<td>^</td>
<td>^</td>
<td>^</td>
<td>^</td>
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<td></td>
</tr>
<tr>
<td>TBG deficiency</td>
<td>^</td>
<td>^</td>
<td>^</td>
<td>^</td>
<td></td>
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</tr>
<tr>
<td>T4 displacement</td>
<td>^</td>
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^ = high  
▼ = low

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|                            |          |          |         |         | ^ if Secondary |
| T3 toxicosis               | Normal   | ^        | normal  | ^       | normal    | ^           |
| Hypothyroid                | ^        | ^        | ^       | ^       | normal    | ^ if primary
|                            |          |          |         |         | ^ if secondary |
| TBG excess                 | ^        | ^        | normal  | normal  | ^         | Normal      |
| TBG deficiency             | ^        | ^        | normal  | normal  | ^         | Normal      |
| T4 displacement by drugs   | ^        | normal   | Normal or ^ | normal | normal | Normal |

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Pituitary Gland 55
Hypothyroidism

TRH

Controlling Gland

Gland

TSH

T₃ + T₄

Target Organ

Coarse, dry, brittle hair

Lethargy and impaired memory

Loss of lateral eyebrows

Periorbital edema and puffy face

Pallor

Deep, coarse voice

Large tongue

Diminished perspiration, cold intolerance

Slow pulse, enlarged heart (cardiomegaly)

Gastric atrophy

Weight gain

Constipation

Peripheral edema (hands, feet, etc.)

Menorrhagia (anovulatory cycles)

Muscle weakness

From Porth and Matfin Pathophysiology – Concepts of Altered Health states 2009
Hypothyroidism

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</tr>
<tr>
<td>Low</td>
<td>Low fT4</td>
<td>High</td>
<td>Raise</td>
<td>But patient has hypothyroidism symptoms Consider thyroid hormone resistance</td>
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Diagnose?
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- **Diagnose?**
Growth hormone

GHRH + Somatostatin

GH-release inhibiting hormone

Growth hormone

Anterior pituitary

Liver

Increased protein synthesis

Bone and cartilage

Increased linear growth

Body organs

Increased size and function

Muscle

Increased lean muscle mass

IGF-1

Adipose tissue

Increased lipolysis

Increased FFA use

Decrease in adiposity

Carbohydrate metabolism

Decreased glucose use

Increased blood glucose

Modified from Porth and Matfin Pathophysiology – Concepts of Altered Health states 2009
Growth hormone Excess

Before puberty ends

Normal proportions

but tall

Gigantism

From anatomy:
Closure of metaphysis
Determine age by bone structure / appearance

From Porth and Matfin Pathophysiology – Concepts of Altered Health states 2009
Growth hormone Excess after puberty

Somatotrophic adenoma of pituitary

Acromegalic face

Hyperostosis (Thoracic vertebrae)

Goiter

Increased size (hands, feet)

Cardiomegaly (hypertension)

Peripheral neuropathy

Abnormal glucose tolerance (secondary to insulin resistance)

Thickened skin (hypertrophy of sebaceous and sweat glands)

Male sexual dysfunction (or menstrual disorders in women)

Degenerative arthritis

Acromegaly
Growth hormone Excess - Tests

Plasma IGF-1 has a long half life = sensitive screening test

Plasma GH

Measure plasma GH after a 75 g glucose load. If plasma GH does not fall below 1mU/L, the diagnosis is confirmed.

Look for tumor MRI, Plasma GHRH.
In adults, GH deficiency rarely causes clinical symptoms.
Growth hormone deficiency

In adults, GH deficiency rarely causes clinical symptoms

Growth velocity normal?

Low birth weight baby?

Consider constitutional or familial short stature

Hypothyroid present?

Consider rare causes?

Consider malabsorption / nutritional disorder

GH deficiency