ABNORMAL PITUITARY FUNCTION

Specialist Portfolio Seminar

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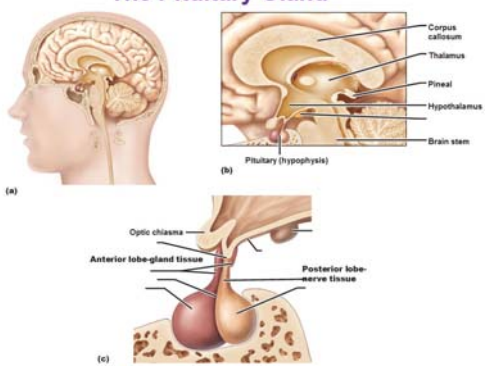
Overview

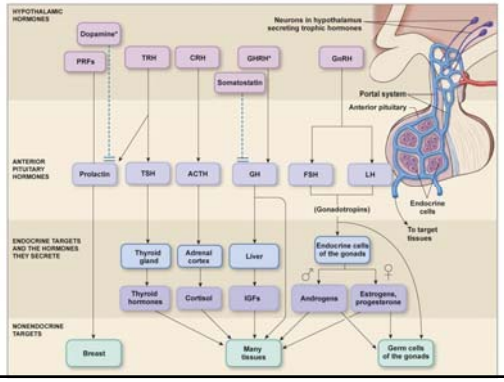
- Anterior pituitary overview
- Posterior pituitary overview
- Pituitary dysfunction (example cases)
- Analytical considerations
- Questions

The Pituitary Gland



http://www.medguidance.com/thread/Pituitary-Gland.html

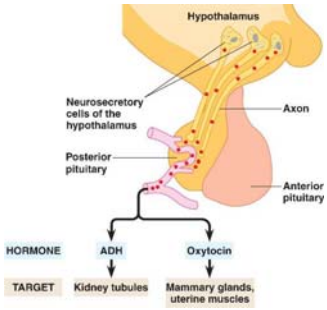
Anterior pituitary systems



Anterior pituitary

Cell type	Hormone secreted	Target organ	Effect on target organ	Release stimulated by	Release inhibited by
Corticotroph	ACTH	Adrenal gland	Production of cortisol	CRH	Cortisol
Lactotroph	Prolactin	Mammary glands	Milk production (in conjunction other hormones)	Suckling TRH	dopamine
Gonadotroph	LH & FSH	Gonads (ovaries / testis)	Production of sex steroids	GnRH	LH & FSH
Thyrotroph	TSH	Thyroid gland	Production of thyroid hormones T4 & T3	TRH	T4 & T3
Somatotroph	GH	Liver	Production of IGF-1	GHRH	somatostatin
		Other tissues	Directly stimulates growth		

Posterior pituitary



http://first-youmedshops.com/posterior-pituitary-hormones.html

Posterior pituitary

Hormone secreted	Target organ	Effect on target organ	Release regulated by
Oxytocin	Mammary gland	Milk ejection	Suckling
	Uterus	Contraction	Stretch receptors
AVP (arginine vasopressin	Renal collecting duct	Resorption of water (insertion of aquaporin water channels)	Osmoreceptors & baroreceptors
	Smooth muscle	Arteriole & capillary vasocontraction, also promotes intestinal contraction	

- N.B. AVP = ADH (anti-diuretic hormone) = vasopressin

Pituitary dysfunction

Disease	Hormone	Excess or deficiency
Anterior hormones:		
Prolactinoma	Prolactin	Excess
Cushing's syndrome (pituitary form)	ACTH	Excess
Acromegaly / gigantism	GH	Excess
Hypopituitarism	One or more pituitary hormones	Deficiency
Growth retardation (uncommon cause)	GH	Deficiency
Posterior hormones:		
SIADH	AVP	Excess
DI (cranial form)	AVP	Deficiency

Case 1

- 32 yr male presents to GP
- Clinical details: TATT, on thyroxine
- Testo very low: 2.0 nmol/L (9.9-27.8)

- LH & FSH added: <1, 2 respectively
- Prolactin added: 9706 miU/L (73-407)
- Cortisol added: 146 *[11am sample – difficult to interpret]*

- *Q: Why is the TSH / fT4 not useful in this case?*

- Macroprolactin added but prolactin result phoned out anyway *– Why?*

Hyperprolactinaemia

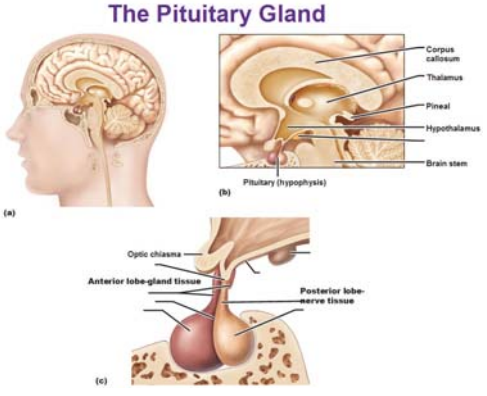
- Variable effects:
  - Amenorrhoea
  - Infertility
  - Galactorrhoea
  - Low libido / impotence

- Q: Why might men usually have larger tumours on presentation?

- If due to a tumour may have direct symptoms from this
  - Headache
  - Visual disturbance

- Q: Why do pituitary tumours cause these symptoms?

The Pituitary Gland



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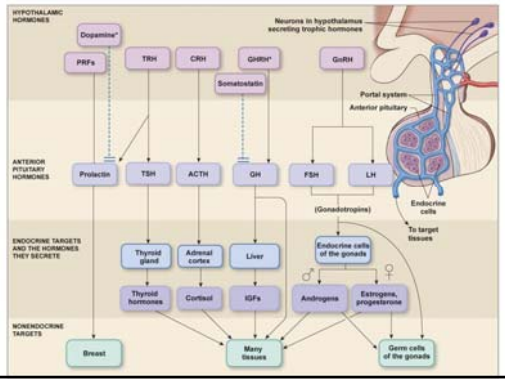
Hyperprolactinaemia

Causes:

- Dopamine antagonists *Why do these cause increased prolactin?*
- Other medications
- Stress
- Pregnancy
- Elevations in PCOS
- Renal failure
- Breast stimulation / chest wall trauma
- Primary hypothyroidism *Why does this cause increased prolactin?*
- Pituitary adenoma
  - Prolactin secreting
  - Compression of stalk and inhibition of dopamine action on pituitary

Anterior pituitary systems



Macroprolactin

- IgG complex with prolactin
- Low bioactivity, i.e. no pathological consequences

- Laboratory artefact
- Should be screened to avoid unnecessary investigations

Method:

- Precipitate any high MW complexes with PEG (polyethylene glycol)
- Measure prolactin pre- and post- PEG (accounting for dilution)
- Check recovery of prolactin in the sample

Diagnosis of prolactinoma

- Exclude other causes:
  - Pregnancy
  - Medication

- Imaging – MRI pituitary
  - Size defines as macroprolactinoma or microprolactinoma

Q: any possibilty of confusion with “macroprolactin” here?!

- Pituitary screen

(check for co-secretion or for loss of function)

  - Prolactin
  - TSH & fT4 Q: why both?
  - Cortisol
  - LH & FSH
  - IGF-1

Treatment

- Medical
  - dopamine agonists Q: Why does this work?
- Surgical
- Radiotherapy

- Combinations

- Follow up

Case conclusion

- Diagnosed with microprolactinoma
- Treated with cabergoline
- Symptomatically improved
- Prolactin now 149 mIU/L

Case 2

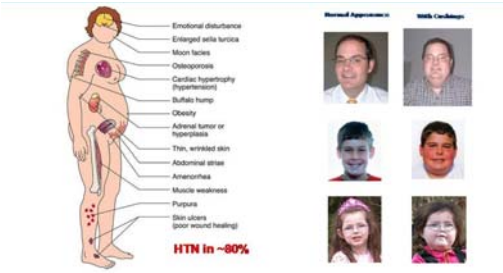
- A previously healthy male patient is diagnosed with hypertension at their GP. They have some baseline bloods:

Na:	143 mmol/L	(133-146)
K:	3.0 mmol/L	(3.5-5.3)
Creatinine:	60 µmol/L	(44-133)

- On examination the patient shows central obesity with purple stretch marks on their abdomen
- The patient reports weight gain over the past year or so
- The patient mentions that they bruise easily

- In view of the history and results the GP organises some further tests…

Cushing's syndrome



http://www.veomed.com/files/powerpoints_images/node314354/Slide4.JPG

Cushing's syndrome

- Syndrome i.e. different causes:
  - Pituitary – ACTH secreting tumour = Cushing's disease
  - Adrenal – cortisol secreting tumour
  - Ectopic ACTH production
  - Exogenous corticosteroids

Diagnosis

1. Confirm excess cortisol:
- 24 hour urinary cortisol excretion
- Midnight salivary cortisol (lose circadian rhythm)
- Low dose dexamethsone suppression test (DST)

2. Measure ACTH:
- Low = appropriate: suggestive of adrenal tumour
- Normal - High = inappropriate: suggestive of excess ACTH (pituitary or ectopic)

3. Further dynamic function testing:
- High dose DST: suppression seen in ~50% pituitary adenoma. No response if ectopic ACTH or adrenal tumour

4. Imaging: Pituitary MRI
- Pituitary lesion present?

Treatment

- Pituitary tumour:
- Surgery / radiotherapy

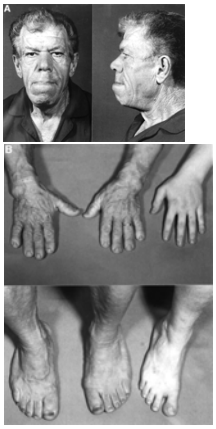
- If co-secretes prolactin may respond to medical therapy to shrink tumour first

Case 3

- 45 yr old female patient presents to their GP due to headaches
- They also mention that their foot size is increasing and their rings no longer fit
- The GP notices that their teeth are slightly spaced on their lower jaw
- The GP suspects acromegaly (GH excess)

Acromegaly

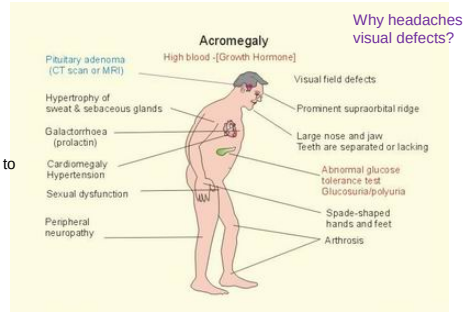
- Overgrowth of skeleton & soft tissue
- Jaw, forehead, hands, feet, tongue



Gigantism
- If GH excess before long bone growth complete
- Increase in linear growth also observed

http://www.physio-pedia.com/Acromegaly

Why headaches & visual defects?



Important to recognise and treat

Diagnosis

- Excess GH
- But… GH secretion episodic & pulsatile
- Therefore single measurement of GH not helpful

→ Use IGF-1 as an indicator of GH status

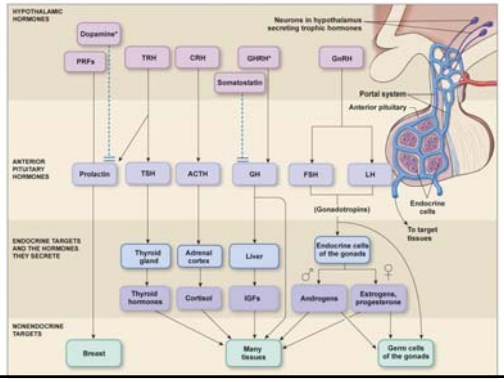
- Dynamic function testing: OGTT.
  - Glucose load should suppress GH
  - Acromegaly: GH does not suppress

Treatment

- Surgery
- Medical treatment:
  - Dopamine agonists (if co-secretes prolactin)
  - Somatostatin analogues
  - GH-receptor antagonist: pegvisomant

Why do these work?

Anterior pituitary systems



Case 4

- A 50 yr old male patient was diagnosed with a prolactinoma
- Following treatment with cabergoline to shrink the tumour he underwent pituitary surgery

- What is he now at risk of?

Hypopituitarism

- Deficiencies in one or more of the pituitary hormones

Causes:

- Pituitary or non-pituitary tumours
- Infiltrative processes e.g. sarcoidosis, haemochromatosis
- Infections e.g. cerebral abscess, meningitis, syphilis.
- Ischaemia and infarction e.g. Sheehan's syndrome (postpartum haemorrhage), pituitary apoplexy (caused by an acute infarction of a pituitary adenoma)
- Iatrogenic e.g. irradiation, neurosurgery
- Head injury (may have occurred up to several years before)
- Autoimmune

Case: post pituitary surgery

- Check remaining pituitary function
- May be transient or permanent loss of function in one or more axis

- Q: What is the most important pituitary hormone system to check?

- ACTH: check by measuring 9am cortisol and SST if necessary
- If cortisol is low: steroid cover
- Recheck for recovery later

- Remaining axis should be tested ~1 month post surgery

- N.B. Post-irradiation pituitary function should be assessed regularly (~6 monthly)

Diagnosis of hypopituitarism

- Dependent upon patient history for degree of investigation

Example first line screen:
- 9 am cortisol
- TSH & fT4 Why both?
- Pitiuitary-gonadal axis:
  - Females – regular menstrual cycle indicates intact axis
  - Otherwise check LH/FSH & oestradiol in females
  - Check LH/FSH & testosterone in males
- Prolactin
- Serum Na

Case 5

- Patient in hospital with pneumonia
- Persistent hyponatraemia

- Results:

Serum Na	126 mmol/L	(133-146)
Serum osmolality	258 mOsm/kg	(275-295)
Urine osmolality	300 mOsm/kg	(50-1500)
Urine Na	60 mmol/L	

- Are the urine results appropriate? Why not?

SIADH criteria

- Most common cause of hyponatraemia in hospitalised patients BUT other causes must be ruled out

Criteria for diagnosis:
- Clinically euvolaemic patient
- Patient not on diuretics
- Hyponatraemia with low serum osmolality
- Normal renal, adrenal and thyroid function
- Urine osmolality less than maximally dilute
- Inappropriately high urine sodium (e.g. >40 mmol/L)

SIADH

- Inappropriate AVP i.e. retention of water despite low serum osmolality & normal/increased plasma volume

Common causes
- Many drugs including tricyclic antidepressants, carbamazepine, omeprazole, vincristine, ACE inhibitors, narcotics, nicotine
- Post-operative stress
- CNS disturbances e.g. infections, stroke, trauma
- Pulmonary disorders e.g. pneumonia, tuberculosis, emphysema

Treatment

- Fluid restriction
- Underlying cause
- V2 receptor antagonist

Case 6

- A patient presents to their GP complaining of excessive urination.
- On questioning, the onset followed a car accident where they suffered a head injury.
- The GP organises some tests:
  - Serum ??
  - Urine ??
- Serum U&E's are normal
- 24 hour urine collection comprises 6 L

Diabetes Insipidus

Two types:

- Central or Cranial DI (deficient AVP production)
- Nephrogenic DI (resistance to AVP)
- Can be inherited or acquired

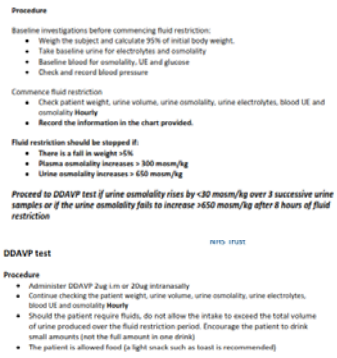
Differential diagnosis:

- Psychogenic polydipsia
- Osmotic diuresis

Diagnosis DI

- Confirm high urine output (distinguish frequency / volume)
- Baseline tests:
  - Serum U&E
  - Serum osmolality
  - Early morning urine osmolality
    N.B. early morning may help distinguish if excess water intake
- Exclude other causes:
  - HbA1c / fasting glucose – diabetes
  - 9am cortisol – adrenal insufficiency
  - TSH – thyroid dysfunction

Water deprivation test



Procedure

Baseline investigations before commencing fluid restriction:

- Weigh the subject and calculate 95% of initial body weight.
- Take baseline urine for electrolytes and osmolality
- Baseline blood for osmolality, UE and glucose
- Check and record blood pressure

Commence fluid restriction

- Check patient weight, urine volume, urine osmolality, urine electrolytes, blood UE and osmolality **Hourly**
- **Record the information in the chart provided.**

Fluid restriction should be stopped if:

- **There is a fall in weight >5%**
- **Plasma osmolality increases > 300 mosm/kg**
- **Urine osmolality increases > 650 mosm/kg**

Proceed to DDAVP test if urine osmolality rises by <30 mosm/kg over 3 successive urine samples or if the urine osmolality fails to increase >650 mosm/kg after 8 hours of fluid restriction

DDAVP test

Procedure

- Administer DDAVP 2ug i.m or 20ug intranasally
- Continue checking the patient weight, urine volume, urine osmolality, urine electrolytes, blood UE and osmolality **Hourly**
- Should the patient require fluids, do not allow the intake to exceed the total volume of urine produced over the fluid restriction period. Encourage the patient to drink small amounts (not the full amount in one drink)
- The patient is allowed food (a light snack such as toast is recommended)

SWBH protocol

Water deprivation test

Interpretation of Water deprivation test

Post dehydration Osmolality (mOsm/kg)		Post DDAVP Osmolality (mOsm/kg)	Diagnosis
Plasma	Urine	Urine	
283-293	>750	>750	Normal
>293	<300	<300	Nephrogenic diabetes insipidus
>293	<300	>750	Cranial diabetes insipidus
<293	300-750	<750	Chronic polydipsia
<293	300-750	>750	Partial nephrogenic DI or primary polydipsia

Treatment

- Cranial DI: replace the hormone
  - DDAVP
- N.B. Nephrogenic DI cannot do this
  - Manage water intake

Pre-analytical considerations

- ACTH
  - Rapidly degraded →Use cortisol to test axis
  - Sensitive to freeze-thaw cyles
- AVP
  - Rapidly degraded
  - Limited assays available, no standardisation
- Circadian rhythms
  - Cortisol as a measure of ACTH function
- Pulsatile secretion
  - GnRH & LH, GH

Analytical considerations:

All are peptide hormones:

- Prolactin
- GH
- ACTH
- AVP
- Oxytocin

Some are glycoproteins:

- FSH
- LH
- TSH

share alpha subunit, also hCG

Assays

- 2 site immunoassays

Interferences:

- Hook effect
- Macroprolactin

Standardisation Why does this matter?

- Standardisation challenging for peptide hormones
- Definition of standard material – different circulating forms
- Immunoassays: different manufacturers use different antibodies against different epitopes
- Different buffers etc

Standardisation

E.g. GH

- Different forms
  - ~75% circulates in original 22kDa form
  - Also post-translation modification: 20kDa form
  - Also dimers and complexes with binding protein
- Assays now standardised to 22kDa form but may still show different cross-reactivity
- Method-specific cut-offs should be used for interpretation
- Also differing glycosylation of circulating glycoproteins to recombinant standards e.g. LH, FSH

Rarely measured

AVP

- Stability
  - sample must be separated & stored frozen until analysis
- Limited assay availability, RIA
- Long TAT
  - Useful?
- Standardisation?!

Oxytocin

- No relevance to reproductive disorders

Knowledge assessment to follow…