

Adrenal suppression

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ADRENAL SUPPRESSION: following long-term corticosteroid therapy


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Cambridge



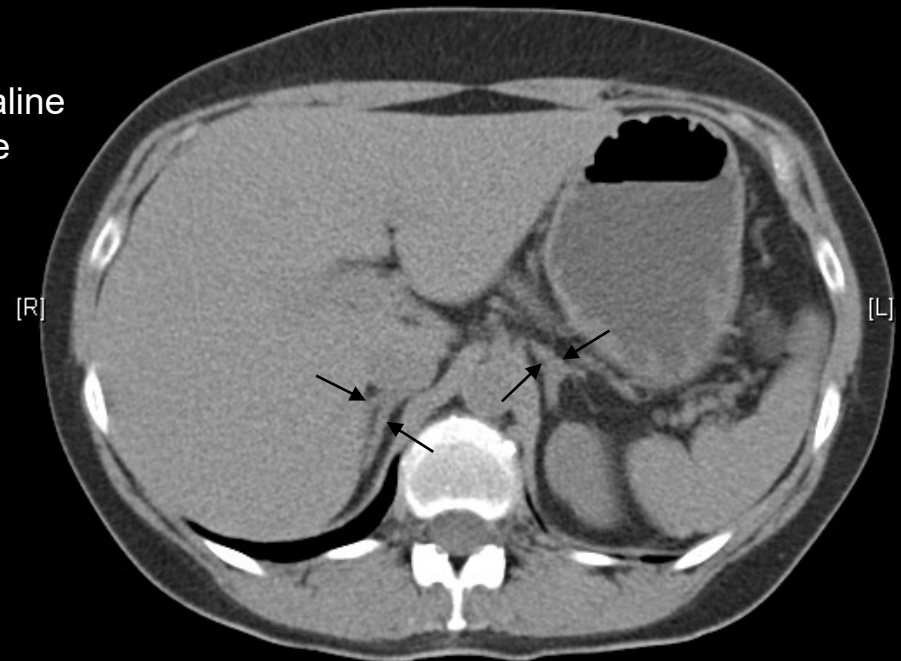
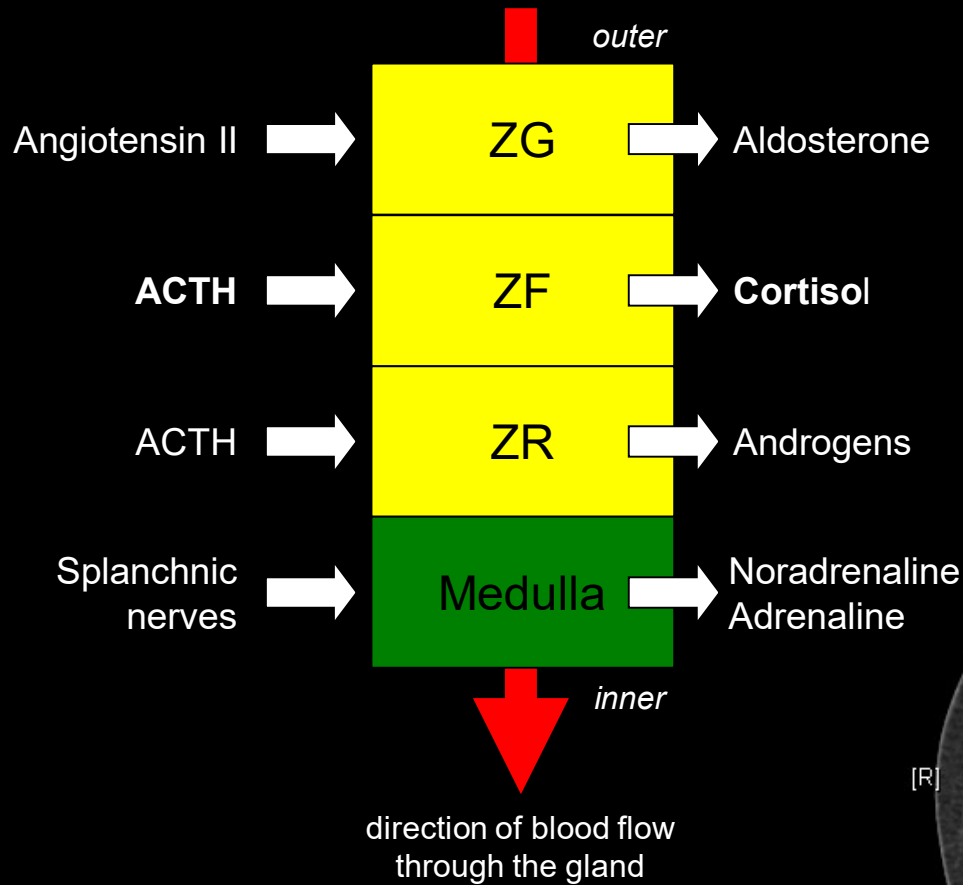
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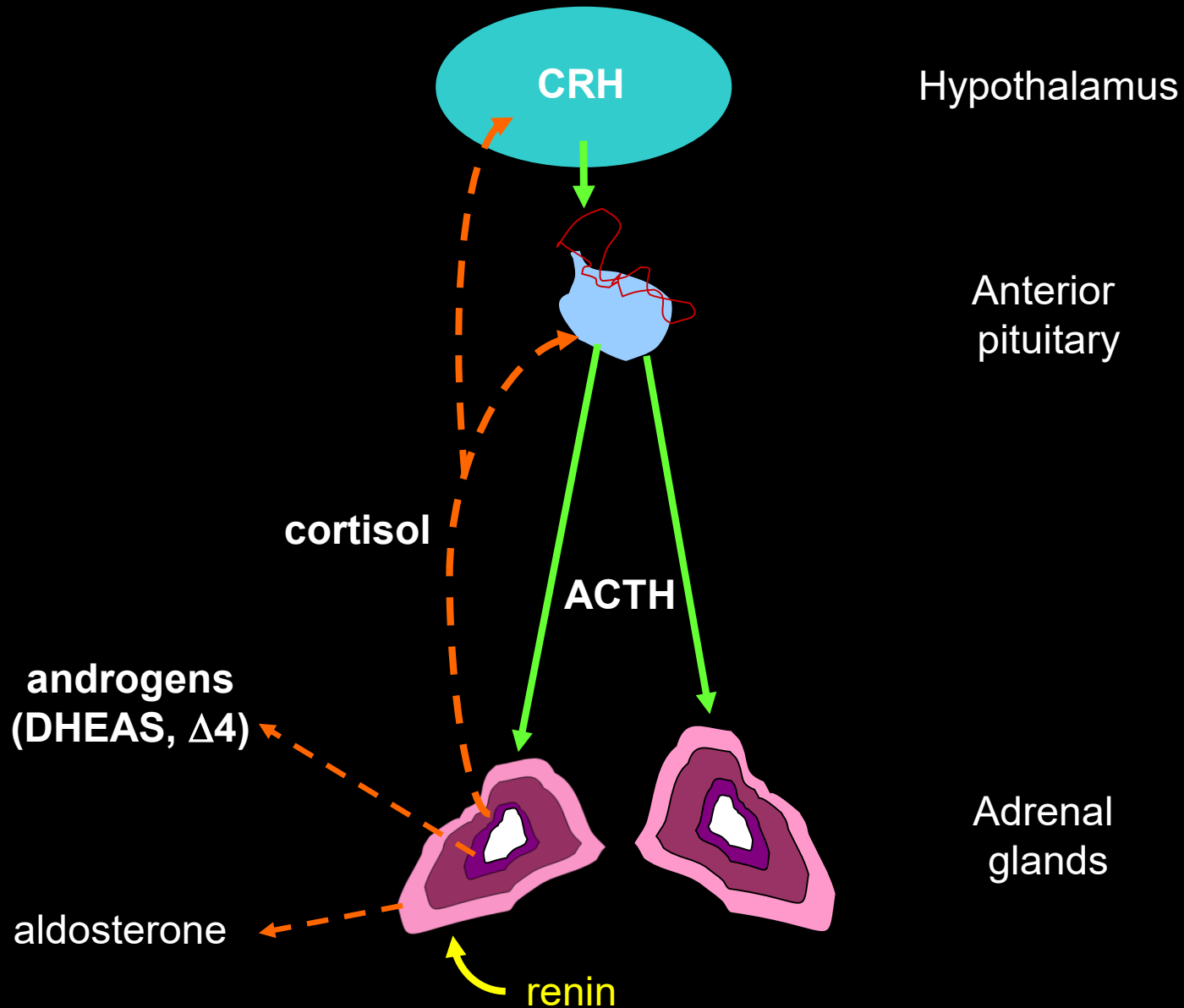
Disclosures

AstraZeneca
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Adrenal production of cortisol



Regulation of cortisol production – HPA axis



Circadian (diurnal) rhythm of cortisol secretion

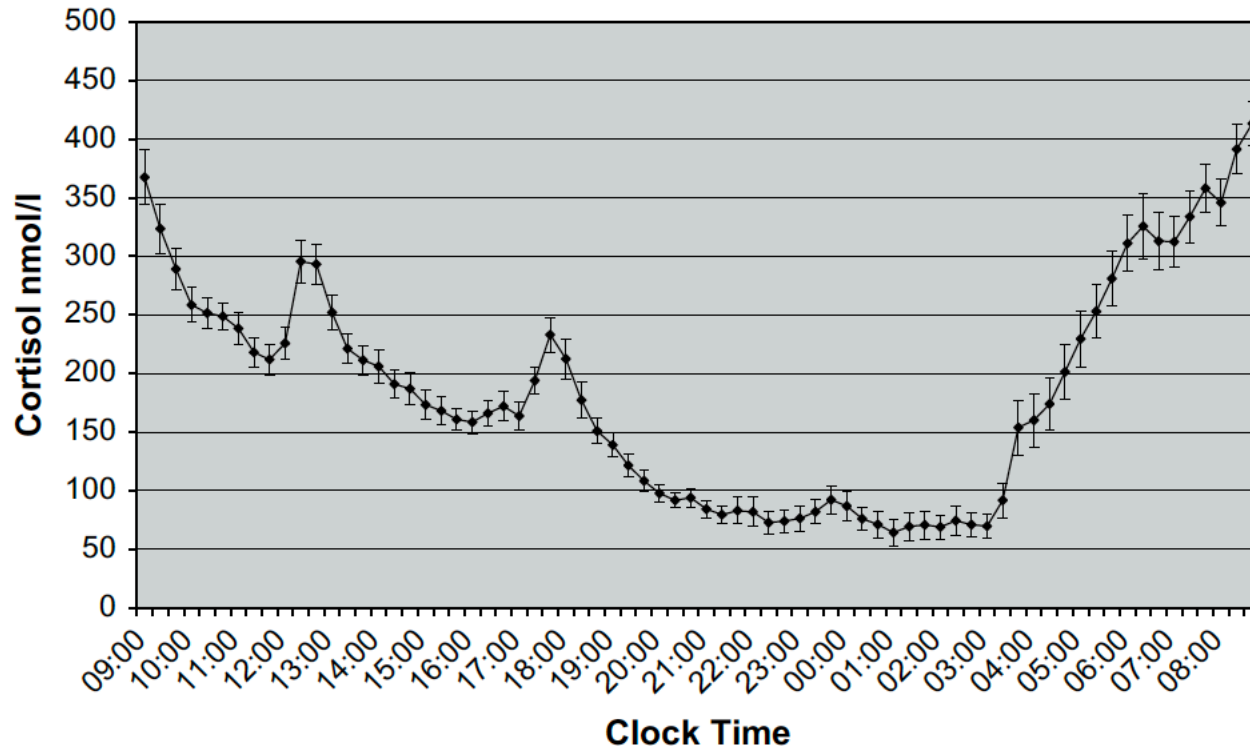


Fig. 1. Circadian rhythm of cortisol (Mean \pm SEM) in 33 individuals with 20-minute cortisol profiling.

HPA dysfunction – the challenges...

HPA dysfunction is frequently insidious and protean, and is therefore easily overlooked...

BUT

Significant time and effort is expended in inappropriate investigation of the HPA axis with misleading or uninterpretable results...

Glucocorticoid excess

Too much of a good thing

- Cardiovascular
- Metabolic
- Homeostatic
- Immunologic/anti-inflammatory



Clinical Features of GC excess

Obesity, weight gain

Facial plethora and change of facies

Skin thinning and easy bruising, striae, interscapular fat pad

Reduced libido, menstrual irregularities

Hypertension

Hirsutism

Depression, emotional lability, disturbed sleep

Glucose intolerance & diabetes mellitus

Weakness, proximal myopathy

Osteopenia, fractures

Venous thromboembolism

Oedema

Glucocorticoid deficiency

Glucocorticoids are essential

- Cardiovascular
- Metabolic
- Homeostatic
- Immunologic/anti-inflammatory

'HIGH STAKES'

Clinical Features GC deficiency

Hypotension (esp. postural)

Inability to mount stress response

Generalised weakness, aches & pains

Hypoglycaemia

Shock, fever in crises

Tiredness / fatigue

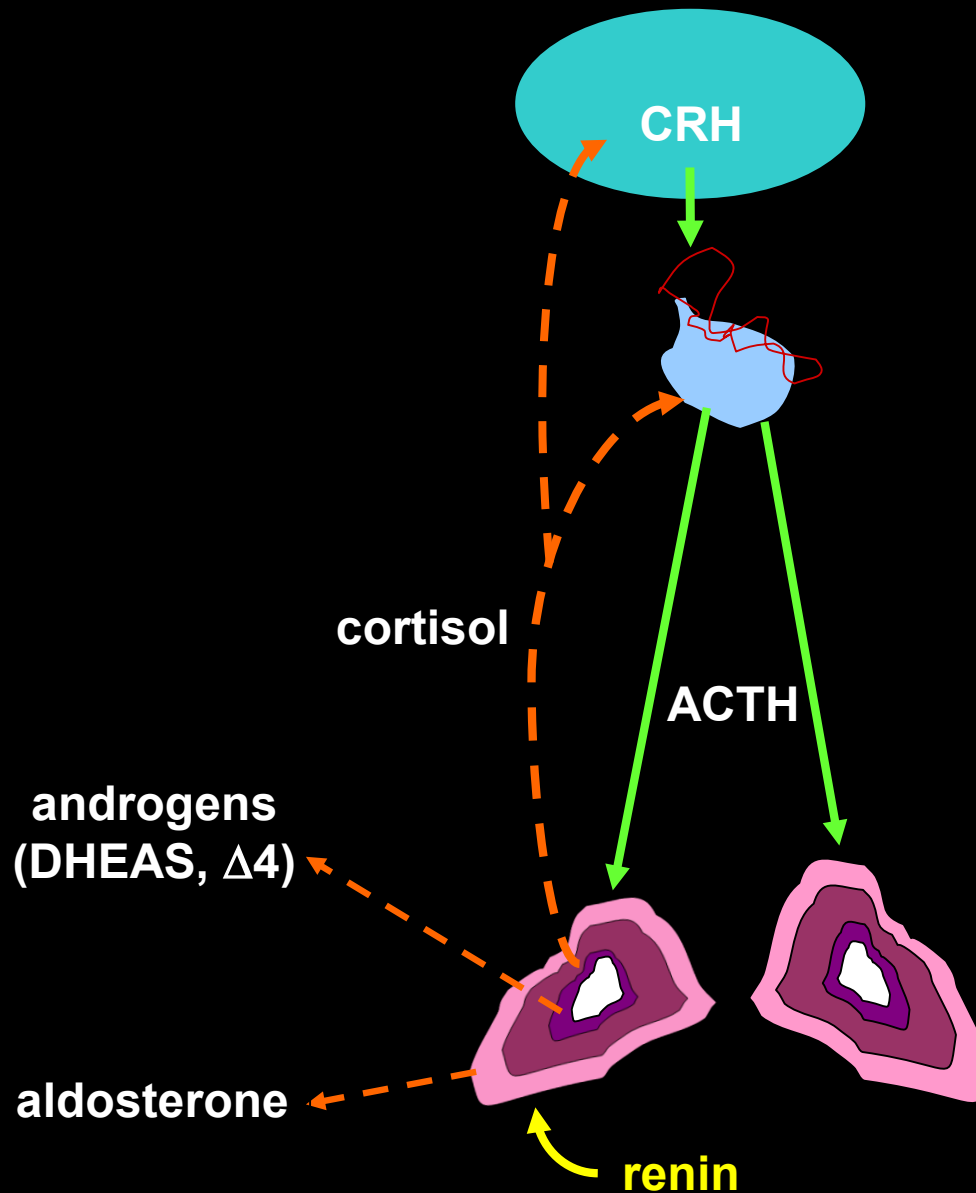
Anorexia, weight loss, N&V, GI upset

K

Electrolyte disturbance [hypoNa⁺
(± hyperK⁺ if primary adrenal failure)]

S

Disorders of the hypothalamic-pituitary-adrenal axis

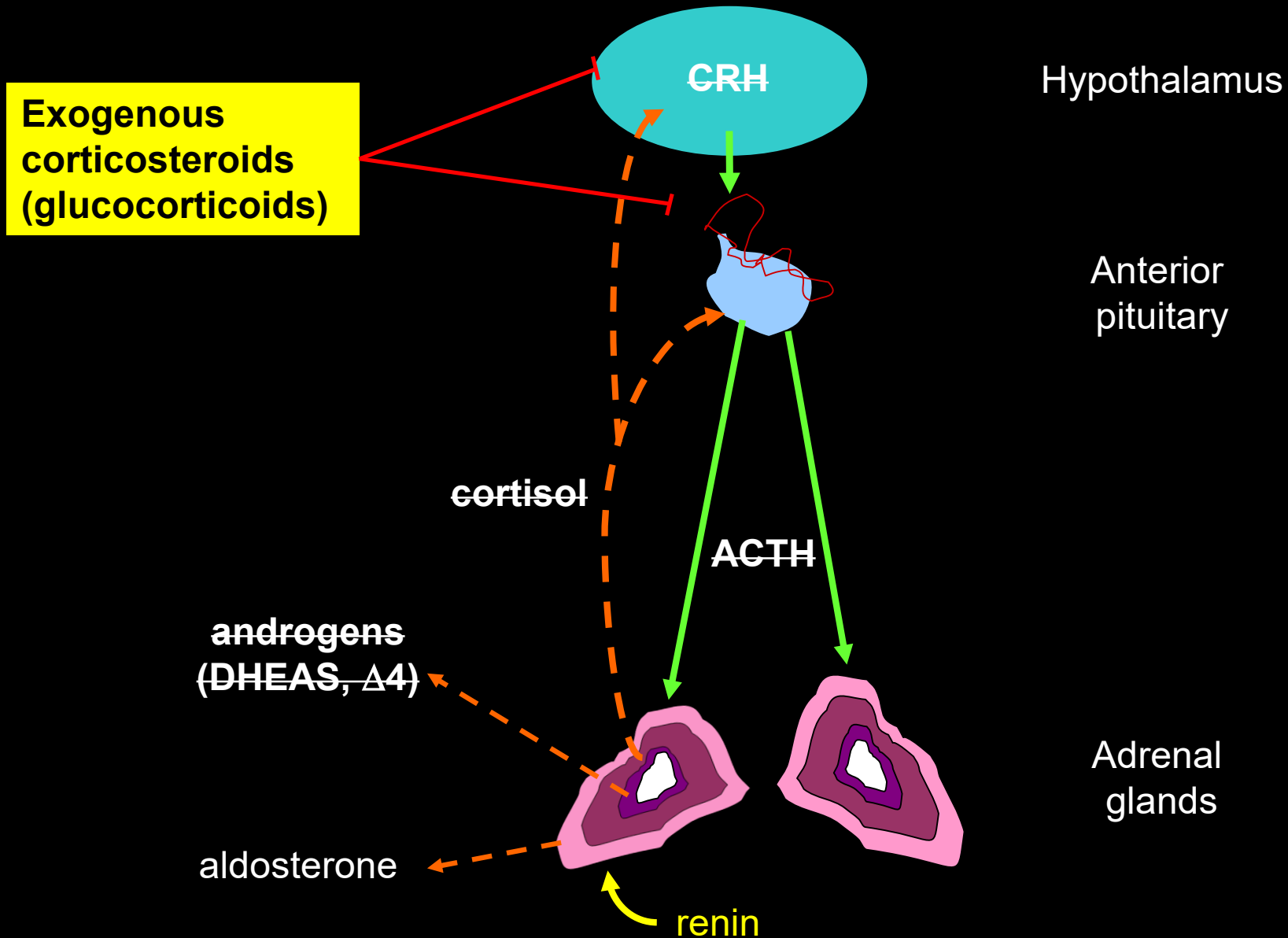


Radiotherapy
Infiltrative Disorders
Tumours
Genetic disorders

Adenomas
Meningiomas
Genetic disorders
Infarction
Hypophysitis
Apoplexy
Metastases

Autoimmunity
TB
Haemorrhage
Metastases
Genetic Disorders
(X-linked, e.g. ALD)

HPA axis suppression by exogenous glucocorticoids



Glucocorticoid equivalent dosages

20mg hydrocortisone / day

≈

?mg prednisolone / day

≈

?dexamethasone / day

Glucocorticoid equivalent dosages

20mg hydrocortisone/day (given as *b.d.* or *t.d.s.* regimen;
some mineralocorticoid activity)

≈

5–7.5mg prednisolone/day (given as *o.d.* or *b.d.* regimen;
minimal mineralocorticoid activity)

≈

0.5–0.75mg dexamethasone (typically given as *b.d.* regimen;
no mineralocorticoid activity)

HPA axis suppression – at risk groups

When to consider?

Groups at risk of HPA suppression

Recent repeated courses of OCS
(especially if taken for >3 weeks)

Taken a short course within 1 year of
stopping long term OCS

Received >40mg daily prednisolone
or equivalent

Received >3 weeks of treatment

Repeated doses in the evening

Other possible causes of adrenal
insufficiency

HPA suppression by exogenous corticosteroids

Remember:

- Individual susceptibility to HPA axis suppression and rate and extent of recovery of adrenal function following withdrawal of exogenous corticosteroids (oral, inhaled or topical), is extremely variable
- Taking oral corticosteroid in the morning and alternate day therapy may lessen the likelihood of adrenal suppression

Which test(s)?

Potential investigations for HPA axis suppression

- Serum cortisol
- Plasma ACTH
- Short synACTHen test
- Depot synACTHen test
- Insulin tolerance test

Serum (total) cortisol – what does it mean?

- Truly random cortisol has limited value
 - 9 AM cortisol provides some indication of HPA function:
 - $>350\text{nmol/L}$: excludes significant adrenal insufficiency*
 - $<100\text{nmol/L}$: likely subnormal HPA function
 - intermediate values equivocal...
 - Late night cortisol useful in Ix of Cushing's syndrome
- * assuming no confounding cortisol binding globulin (CBG) effects, e.g.
- oral oestrogen therapy
 - pregnancy
- which can yield falsely reassuring or falsely concerning results

Short synACTHen testing

- 250mcg synacthen i.m. or i.v. at 09:00 hours
- Serum cortisol pre (0 minutes) and post [30 minutes (\pm 60 min)] injection
- **Basal ACTH** only informative if adrenal function unequivocally subnormal – *therefore do not measure unless advised to do so by Endocrine team*
- Limited validation for use in hypothalamic and pituitary disease through comparison with “gold standard” insulin tolerance test

Short synACTHen testing – potential pitfalls

- Less information when not undertaken at 09:00 hours
- Lower sensitivity for hypothalamic or pituitary disease
[esp. with recent damage (within 6 weeks); reflecting the trophic vs secretagogue effects of ACTH]

HPA suppression by exogenous corticosteroids

SST:

- is not needed in many corticosteroid-treated patients in whom axis suppression is unlikely or not suspected
- should only be undertaken when the corticosteroid dose has been tapered to a physiological replacement level, to assess whether or not the axis is suppressed, with this determining the rate at which corticosteroid replacement can be further reduced or even discontinued
- in a patient whose axis is known to be suppressed, may be used to assess whether the HPA axis is recovering, and to guide the tempo of further withdrawal of corticosteroid replacement

HPA suppression by exogenous corticosteroids

- An SST is not usually indicated in the following circumstances:
 - patients continuing on oral corticosteroid in a dose equivalent to or above physiological levels
 - patients undergoing short courses (<3 weeks) of corticosteroid therapy (unless repeated course in a short timeframe)
 - patients on low dose corticosteroids (oral, inhaled or topical)

HPA suppression by exogenous glucocorticoids

- As with all endocrine tests, results must be interpreted in the clinical context;
 - a subnormal SST with symptoms (asthenia, fatigue, dizziness), may suggest a need for partial or full glucocorticoid replacement, with periodic testing to gauge axis recovery and the tempo of steroid withdrawal
- The HPA axis may remain chronically suppressed in patients who have received long-term corticosteroids
- Patients with a slightly subnormal SST, but no symptoms, may not require regular replacement, but should be advised to take supplementary glucocorticoid (e.g. hydrocortisone 5mg *b.d.*) during intercurrent illness ('Sick day rules')

Oral corticosteroid (OCS) reduction

Safe withdrawal of OCS

- From an **endocrine** perspective OCS can be safely reduced to physiological levels (e.g. 5–7.5mg prednisolone daily)
- Tapering below 5mg/day in groups at risk of HPA axis suppression may be informed by dynamic testing (e.g. SST)

SST

- Should only be undertaken when the OCS dosage has been tapered to physiological replacement levels
- 9 am cortisol may be a useful first step (*i.e.* before performing SST)
- Informs the rate at which OCS may be further reduced or stopped
- May inform recovery in patients known to have HPA axis suppression
- Not advised in patients on greater than physiological OCS or in those who do not fit into one of the 'at risk' groups

SST

Interpretation of SST*

0 minutes cortisol (9am basal: nmol/L)	30 minutes cortisol (peak; nmol/L)	Category	Action
<100	<250	AI	Full replacement & sick day rules
100-350	250-450	Partial AI	Sick day rules +/- partial replacement
>350	>450	Normal	None

*Always confirm local thresholds

Cautions & other measures

- Most sensitive when performed at 0900 hours
- CBG effect from oral oestrogen, pregnancy may misleadingly elevate results
- Symptoms of AI may suggest need for OCS over and above interpretation of the numbers
- Usually not interpretable on supraphysiological OCS
- Patients with partial or full AI should carry a steroid alert card, extra OCS and consider a MedicAlert bracelet and an emergency injection pack

HPA suppression by exogenous corticosteroids

- Individuals with a subnormal SST, but who require ongoing topical or inhaled corticosteroids which are not detected in most laboratory cortisol assays, present a specific challenge
- To cause HPA axis suppression, such corticosteroid is being absorbed systemically, and therefore exerting a glucocorticoid effect
- However, there is no readily available, biochemical method to measure systemic glucocorticoid ***effect***

And don't forget...

- 'Sick Day Rules'
- 'Steroid Card'
- Medical Alert system
- Emergency ('Rescue') Pack

Questions?