Adrenal Function

- chemistry of steroids/biosynthesis of cortisol, aldosterone & adrenal androgen
- pathophysiology of HPA axis disorders, secondary hypertension
- Laboratory Diagnosis of Cushing’s, adrenal insufficiency, hirsutism/virilism, pheochromocytoma, primary aldosteronism

Adrenal Steroids

- glucocorticoids & mineralocorticoids are 21-carbon steroids
- androgens are 19-carbon steroids
- adrenal androgens are 17-ketosteroids
- key adrenal androgen is dehydroepiandrosterone sulfate (DHEAS)
- testosterone is a 17-OH steroid - not a ketosteroid

Adrenal Biosynthesis

- cortisol is the result of 3 successive hydroxylations of progesterone at 17, 21 and 11
- aldosterone synthesis requires only 21 and 11 hydroxylation steps
- androgen requires only 17 hydroxylation
Adrenal Pathophysiology

- free plasma cortisol inhibits biosynthesis and secretion of CRK and ACTH
- ACTH is synthesized as a large precursor, pro-opiomelanocortin (POMC)
- ACTH stimulates cortisol, adrenal androgen and under short-lived conditions - aldosterone

Adrenal Insufficiency

- autoimmune adrenalitis
- TB & systemic fungal infections
- AIDS & opportunistic infections
- acute hemorrhage or thrombosis (sepsis, anticoagulant therapy, antiphospholipid syndrome, clotting disorders0
- hypothalamic-pituitary disease
- glucocorticoid therapy

Lab Diagnosis: Adrenal Insufficiency

- Ruling out - low probability
  - 8:00 am serum cortisol
  - < 3 ug/dL confirms
  - > 20 ug/dL rules out
  - 8:00 serum cortisol 3 - 20 ug/dL
    - short corticotropin stimulation
- Primary vs Secondary
  - basal serum cortisol & ACTH

Short Corticotropin Stimulation

- 250 ug cosyntropin before 10:am
  - serum cortisol, before, 30 & 60 min post
- a low dose of 1 ug cosyntropin for Asthma patients on inhaled glucocorticoids
- any cortisol value > 19 ug/dL excludes
- insulin hypoglycemia test for inadequate inadequate responses

Cushing Syndrome

- Corticotropin-dependent Percent
  - Cushing’s disease 68
  - ectopic ACTH 12
  - ectopic CRH < 1
- Corticotropin-independent
  - adrenal adenoma 10
  - adrenal carcinoma 8
  - nodular hyperplasia < 2
- pseudo-Cushing <2
Lab Diagnosis: Cushing’s

- Screening
  - 24h urine free cortisol
- Confirmation
  - low dose dexamethasone
  - midnight serum cortisol
- Specific Diagnosis
  - ACTH
  - high dose dexamethasone
  - inferior petrosal sinus sampling

Hirsutism/Virilism

- polycystic ovary syndrome
- idiopathic
- Drugs: minoxidil, cyclosporin, androgens, glucocorticoids, antiepileptics
- 21-hydroxylase deficiency
- Cushing syndrome
- adrenal tumors
- ovarian tumors

Lab Diagnosis: Hirsutism/Virilism

- Basal & Dexamethasone Suppression of
  - serum total testosterone
  - serum DHEAS
  - 17-hydroxyprogesterone
  - serum cortisol
- ACTH stimulated 17-hydroxyprogesterone
- FSH & LH

Lab Diagnosis Hirsutism/Virilism

- Rapidly developing Severe Virilism
  - marked inc in DHEAS indicate adrenal malignancy
  - total testosterone > 300 ng/dL and normal or slight inc in DHEAS indicate ovarian malignancy

Lab Diagnosis Hirsutism/Virilism

- LH:FSH ratios > 2.0 favor polycystic ovary syndrome
  - serum total testosterone < 150 ng/dL makes ovarian malignancy unlikely
  - basal or ACTH stimulated
    17-hydroxyprogesterone > 1500 ng/dL indicate 21-hydroxylase deficiency

Pheochromocytoma:

- 24 hr urine Metanephrines
  - positive interferences
    - imiprimamine, monoamine oxidase inhibitors
  - negative interferences
    - radiographic cotrast media
  - sensitivity: 98 - 99 percent
  - specificity: 98 percent
**Pheochromocytoma**

- **VMA**
  - positive interferences
  - hydroxymandelic acid
  - negative interferences
  - monoamine oxidase inhibitors
- sensitivity: 90 percent
- specificity: 98 - 0 percent

**Pheochromocytoma**

- Catecholamines - urine or plasma
  - positive interferences
  - stress, emotion, exercise, catecholamine containing nasal sprays & bronchodilators
  - highly sensitive; choice in MEA-II or in paroxysmal episodes
  - specificity may be a problem

**Primary Aldosteronism**

- Aldosterone producing Adenoma (APA)
- Idiopathic Hyperaldosteronism (IHA)
Primary Aldosteronism:  
Laboratory Diagnosis

- **Screening:** spontaneous or easily provoked diuretic induced hypokalemia
- **Detection:** serum K, urine K, plasma aldosterone (PAC), plasma renin activity (PRA)
  
PAC:PRA ratio > 20 favors primary aldosteronism

Primary Aldosteronism

- **Confirmation**
  - off antihypertensives, spironolactone, diuretics, estrogen
  - high Na & K intake for 5 days
  - urine aldosterone > 14 ug/d favors disease

- **APA vs IHA**
  - > 33% rise in aldosterone &
  - 18-OHB < 100 ng/dl favor IHA

References

- Orth, DN: Cushing’s Syndrome N Eng J Med 1995; 332:791-803