The Many Faces of Conn’s Syndrome

Most hypertension is Essential Hypertension

Proportion of Essential/Secondary depends on definition of “secondary”

(eg if elevated BMI was a “secondary cause” 75% of patients would have it)

<u>Aetiology of Essential Hypertension is Complex</u>

-Multiple interacting mechanisms but important final common pathway is disordered renal sodium handling

- Primitive tribes with low daily Na intake (< 50mmol) do not get hypertension nor do they experience age-related increase in blood pressure

- 75-80% of individuals with essential hypertension have BMI > 25

Secondary Causes of Hypertension

Basic laboratory evaluation of *all* patients prior to conmencing antihypertensive therapy

12-lead ECG

FBC

Na, K, urea creatinine calcium

Fasting glucose + lipids

T4/TSH

Urine microscopy and albumin/creatinine ratio

When To Suspect a Secondary Cause of Hypertension

(1)Resistant Hypertension

(2)Clinical Clues

Resistant Hypertension Definition

A patient has Resistant Hypertension if BP > 140/90 (or > 130/80 with DM, CKD, or history of cardiovascular disease) despite

Optimal Doses

Of a Minimum of Three

Complementary Antihypertensive Medications

One of which is a Diuretic

Clinical Clues

History
• Polyuria/ nocturia/ muscle weakness
• Difficult hypertension in young women
• Snoring/apnoeas/somnolence
• Headaches/ palpitations/ diaphoresis esp in paroxysms
• Recent onset difficult hypertension in an older individual with peripheral vascular disease or smoker
• Headaches/ palpitations/ diaphoresis esp in paroxysms
• NSAID's/ Non-prescribed medications/ herbal remedies
• Dysthyroid symptoms

Exam
•Cushingoid features
• Bruits
•Radiofemoral delay

•*Lab*
• Low eGFR or abnormal urinary sediment
•Hypokalaemia / hypernatraemia/ alkalaemia/
•Hypercalcaemia
• Abnormal TFT

w1

Secondary (identifiable) Causes of Hypertension

- Chronic kidney disease
- **Primary aldosteronism**
- Renovascular disease
- Sleep apnoea
- Drug induced/ related
- Cushing's Syndrome or steroid therapy
- Phaeochromocytoma
- Coarctation of the aorta
- Thyroid/ parathyroid disease
- (Monogenic causes of hypertension – *rare)*

Slide 8

w1 waltervdm, 11/07/2009

Mr CN: 31 year old previously fit Korean man

Doing Masters Degree in business at Auckland University

Taking no regular medication

Presented to GP complaining of 3 months of increasing polyuria + nocturia – also increasing fatigue

O/E BP 180/110

Labs

FBC normal

Na 148mmol/l K 2.5mmol/l urea + creatinine normal

What is the likely diagnosis?

How to proceed?

Secretion of Aldosterone

Stimulated by Angiotensin 2 and Hyperkalaemia

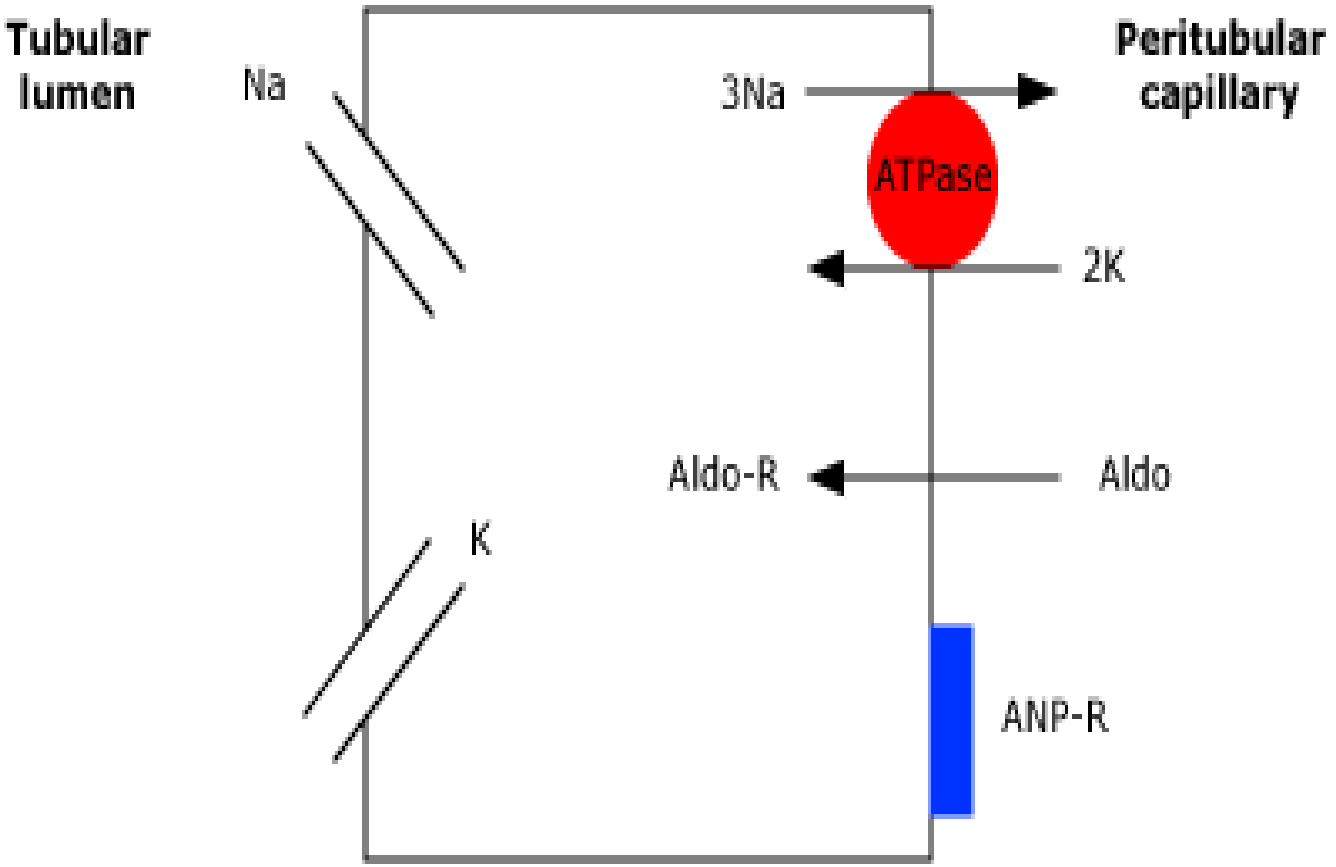
Promotes

- *Sodium reabsorption*

- *Potassium excretion*

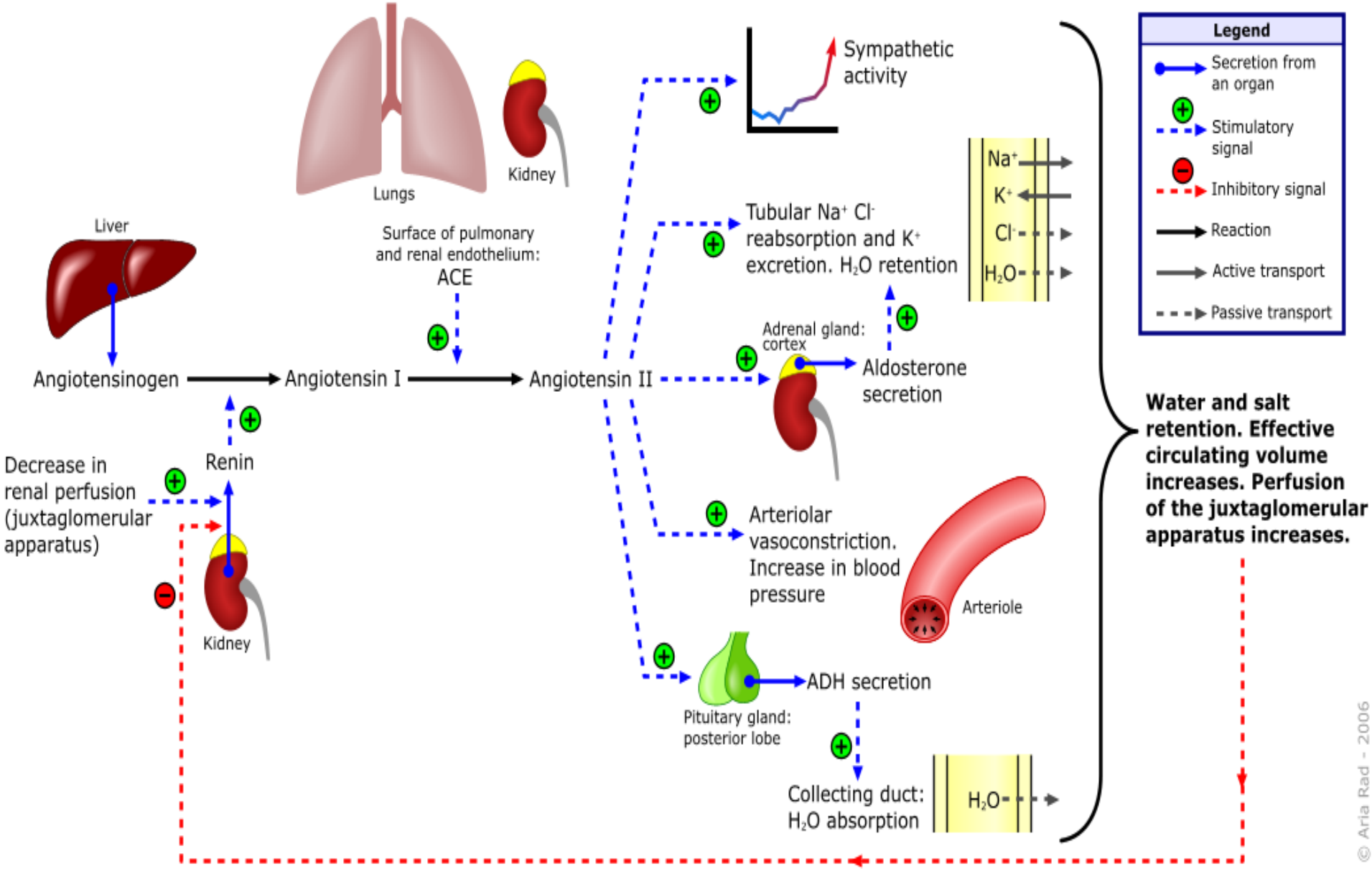
- *Hydrogen ion excretion*

- in the cortical collecting tubule


Tubular lumen
Na
3Na
Peritubular capillary
ATPase
2K
Aldo-R
Aldo
K
ANP-R

It does this by binding the MR (minerallocorticoid receptor) which results in opening of Na channels on the apical membrane of the CCT cell – sodium is pumped into the cell and potassium out.

Renin-angiotensin-aldosterone system



Mr CN: 31 year old previously fit Korean man

Doing Masters Degree in business at Auckland University

Taking no regular medication

Presented to GP complaining of 3 months of increasing polyuria + nocturia – also increasing fatigue

O/E BP 180/110

Labs

FBC normal

Na 148mmol/l K 2.5mmol/l urea + creatinine normal

What is the likely diagnosis?

How to proceed?

Labs repeated at Clinic

Venous Blood
Na 145 mmol/l, K 3.1 Cl’ 101

Arterial Blood Gas
pH 7.48
Base excess +7
Bicarbonate 36 mmol/l
pCO2 6.4kPa
K+ 3.1
Cl- 101mmol/l

..Hypokalaemic (normochloraemic) metabolic alkalosis

Aldosterone …

Aldosterone 950pmol/l (very high) (> 400 is high)

Is this appropriate (secondary aldosteronism) or inappropriate (primary aldosteronism)

If appropriate he has a cause of “secondary hyperaldosteronism” (volume depletion, diuretics, renal artery stenosis, renin-secreting tumour) and plasma renin will be high.

If inappropriate, he has autonomous hypersecretion of aldosteronism (primary aldosteronism) and plasma renin will be suppressed (low or very low)

Plasma renin < 3mU/l (< 10 is low)

So he has primary aldosteronism (probably)….in order to confirm the diagnosis we need to prove that his aldosterone is “non-suppressible”

Saline Suppression Test

2000 ml IV normal saline infused over 4 hours
Aldosterone checked at start and finish
Normal response is for aldosterone to fall < 200pmol/l

Mr CN: pre-saline aldosterone 975 pmol/l
: post – saline aldosterone 850pmol/l

ie non-suppressible

Biochemical diagnosis of primary hyperaldosteronism secured

What are the possible causes of PA??

Primary Aldosteronism (Conn's Syndrome)

Autonomous overproduction of aldosterone by the adrenal glands
1-2% of mild hypertension
Up to 20% of resistant hypertension
Hypokalaemia is a late and variable manifestation;
More than 50% are normokalaemic

Aetiology

- bilateral adrenal hyperplasia (common)
- discrete aldosterone-producing adenoma
- unilateral adrenal hyperplasia (rare)

Mr CN has a CT scan of his adrenal glands which reveals a 1.3cm diameter adenoma of the right adrenal gland.

Will a laparoscopic right adrenalectomy be curative???

Answer ….probably

Why the uncertainty???

(1)Functioning adenomas may be too small to detect with any imaging modality

(2) In bilateral adrenal hyperplasia the adrenal may appear smooth and hyperplastic, nodular, or normal on imaging

(3) The majority of adrenal masses are non-functional

In other words, the only way of being absolutely sure that a unilateral adrenalectomy will be curative is to measure adrenal vein aldosterone concentrations on both sides

If these are markedly elevated on the side of the lesion, diagnosis of functioning adrenal adenoma is confirmed

If there is no strong lateralisation diagnosis of bilateral adrenal hyperplasia is confirmed

Is there any other diagnosis to be considered in patients with primary hyperaldosteronism due to apparent bilateral adrenal hyperplasia?

17 year old boy (JP) from Glen Eden with extended family in Northland presents to ED with a minor sporting injury. BP noted to be 180/110. He is admitted and BP does not settle below 160/90. Auntie says there is a family history of high blood pressure and strokes on his father's side.

Na 144 K 3.1 urea 5 creatinine 80 venous bicarb 31

Renin < 3mU/L (low) Aldosterone 900 ug/l (high)

Saline suppression test - aldo. non-suppressible

CT – no adrenal mass or hyperplasia

Glucocorticoid Remediable Hyperaldosteronism

Suspect in patients with early onset familial hypertension

Biochemically indistinguishable from other causes of Primary Aldosteronism

-Adrenals normal or diffuse hyperplasia on CT

Diagnosis – PCR for the chimeric gene

Treatment

Low dose dexamethasone

Also responds to aldosterone antagonists and amiloride

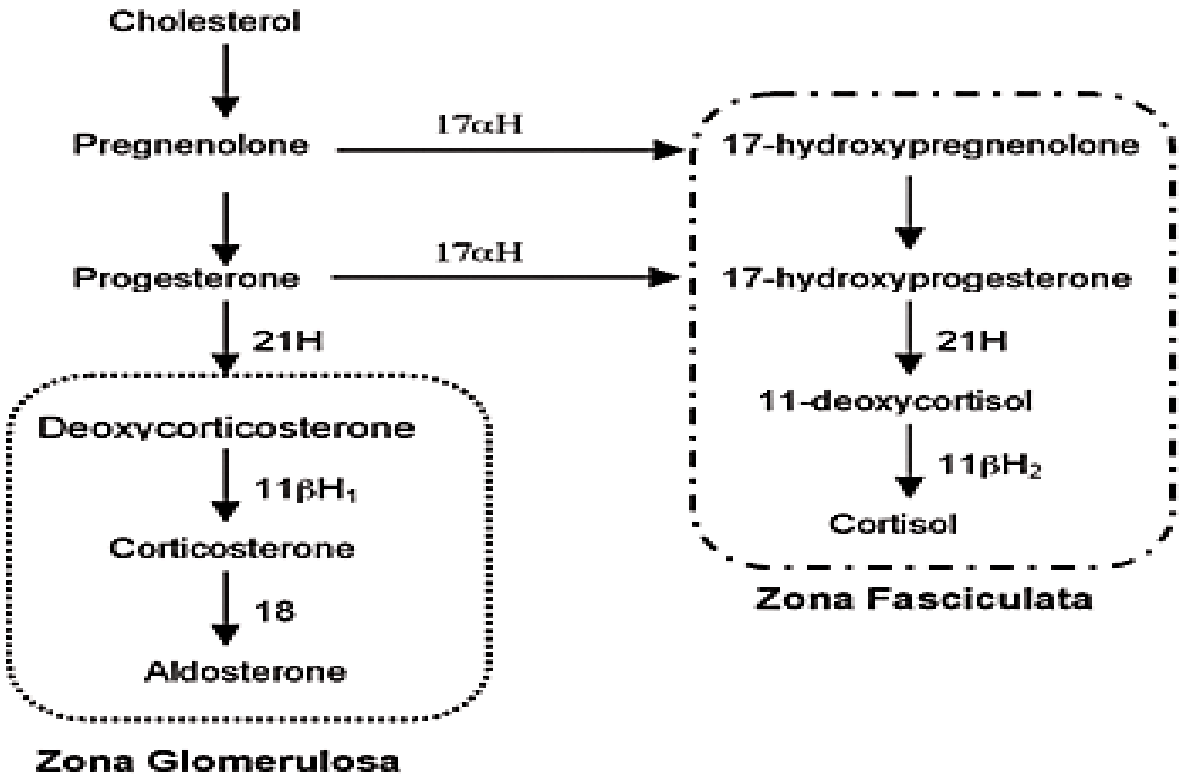
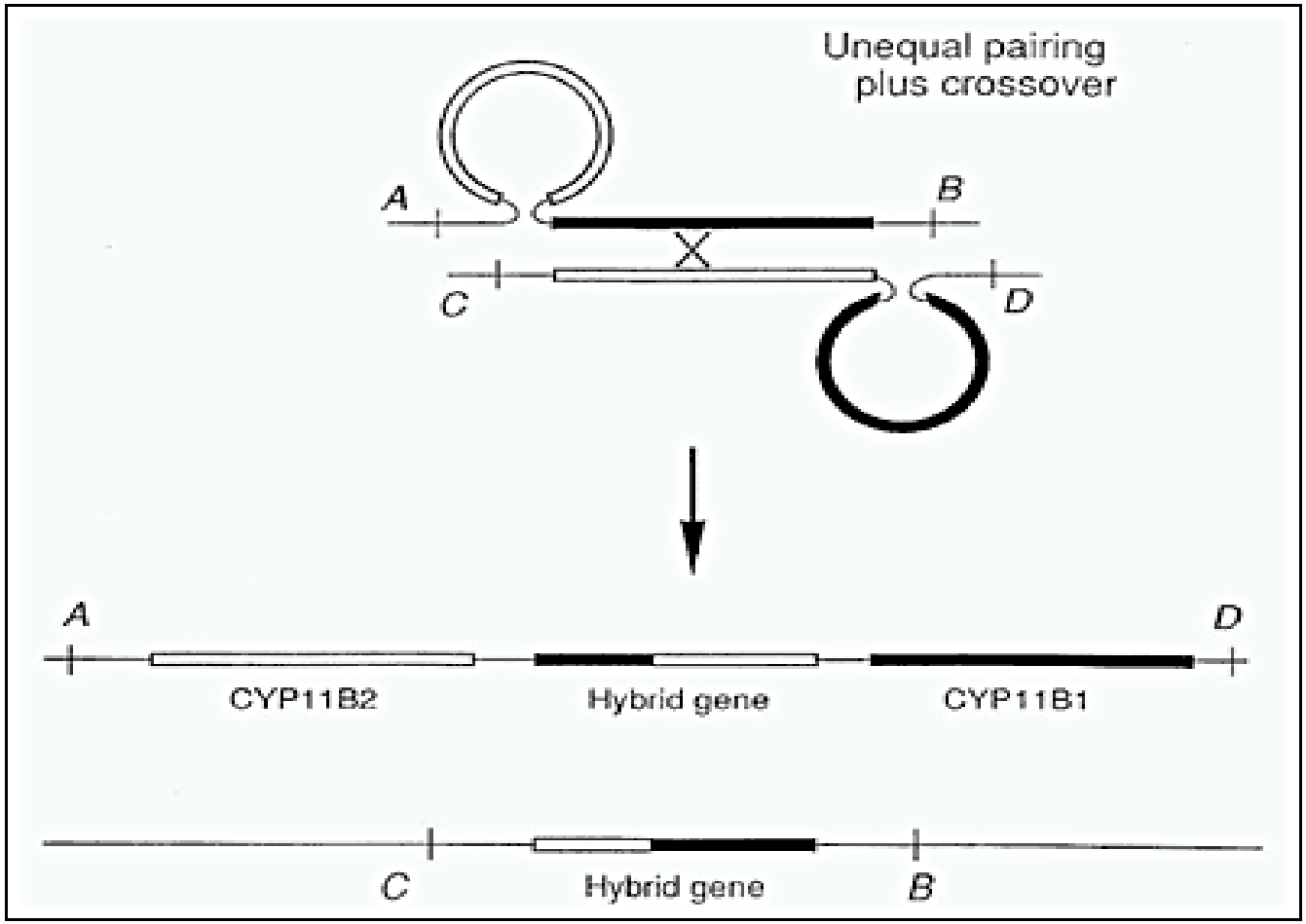


Figure 1. Normal biosynthetic pathways for cortisol and aldosterone. $11\beta H_1$ and aldosterone synthase are present only in the *zona glomerulosa*, and are regulated by angiotensin II. $11\beta H_2$ is present solely in the *zona fasciculata* and is regulated by ACTH. 21H= 21-hydroxylase. $11\beta H_{1\&2}$= 11β-hydroxylase isoenzymes 1 & 2; 18 = 18-hydroxylase/ aldosterone synthase. 17αH= 17α-hydroxylase.

Aldosterone is manufactured exclusively in the Zona Glomerulosa dnd cortisol in the Zona Fasiculata. 11 beta hydroxylase-1 (aldosterone synthase) is found only in the ZG and 11beta hydroxylase 2 only in the ZF.

In GRA there is a chimeric gene transcription located at 8q24 with contains bits of both these enzymes – it is transcriptionally activated by ACTH and present throughout the adrenal cortex. Thus aldosterone secretion is under ACTH rather than aldosterone synthase control.


Unequal pairing
plus crossover
A
B
C
D
A
D
CYP11B2
Hybrid gene
CYP11B1
C
Hybrid gene
B

Diagnostic workup of suspected Primary Aldosteronism

Seated resting mid-morning plasma renin and aldosterone

↓

If suppressed renin (<10mU/l) **+** elevated aldosterone (> 400ug/l) **+** A/R ratio > 40

↓

Saline suppression test (2000 ml IV normal saline over 4 hours with per and post aldosterone)

↓

If post-aldosterone non-suppressible (> 200ug/l)

↓

Adrenal CT scan

↓ ↓

Unequivocal unilateral adenoma > 1.3cm

↓ ↓

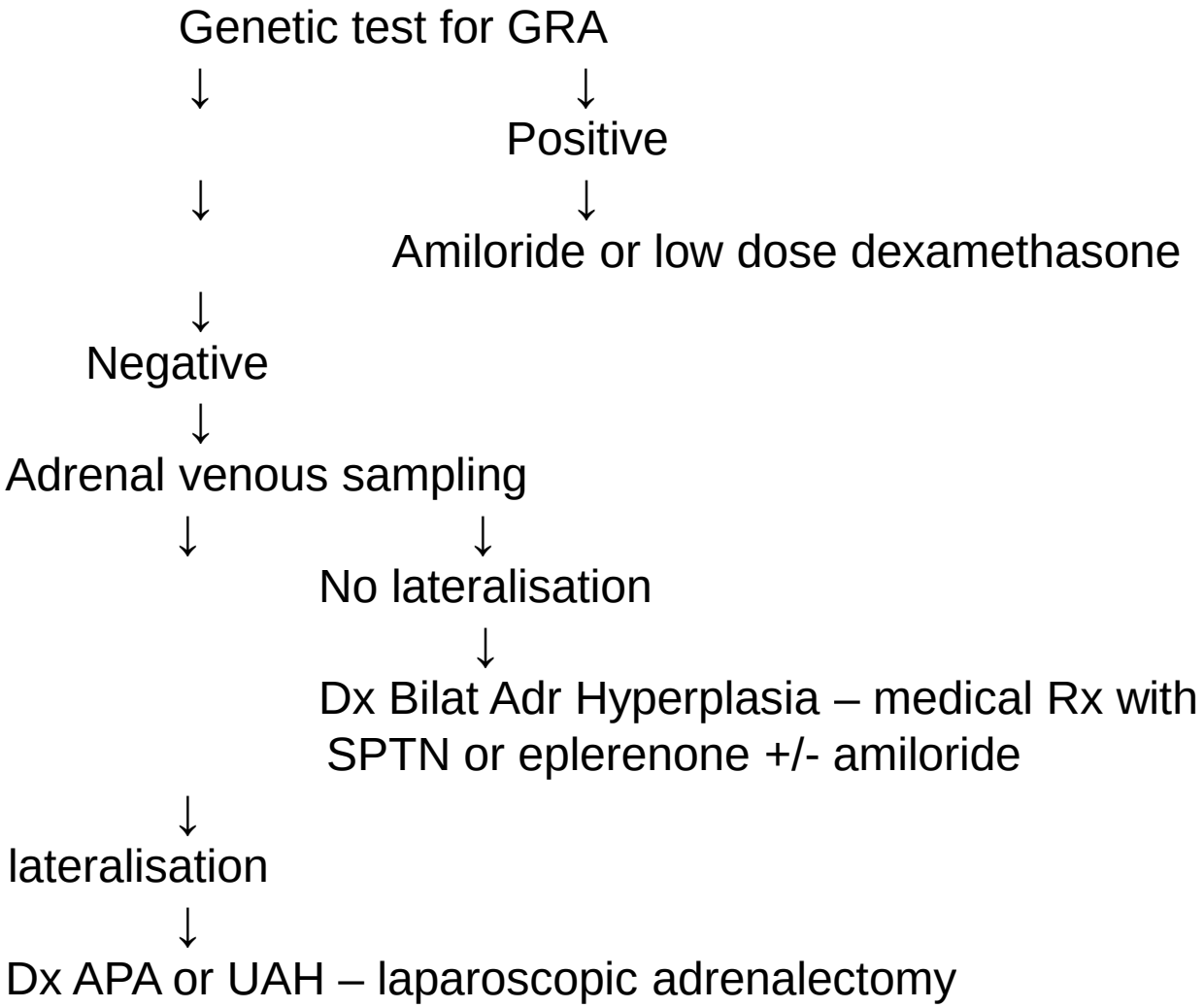
Laparoscopic adrenalectomy

↓

Normal **or** unilateral adenoma < 1.3cm **or** bilateral hyperplasia **or** unilateral hyperplasia

↓

Genetic test for GRA


Genetic test for GRA
Positive
Amiloride or low dose dexamethasone
Negative
Adrenal venous sampling
No lateralisation
Dx Bilat Adr Hyperplasia – medical Rx with SPTN or eplerenone +/- amiloride
lateralisation
Dx APA or UAH – laparoscopic adrenalectomy

Mrs JC: European woman 39 years old

On antihypertensive treatment for several years
Strong family history of hypertension

Referred to Hypertension Clinic because BP uncontrolled on 3 agents (Metoprolol CR190mg daily and *Inhibace Plus* 1 daily) *(Inhibace Plus is a combination of cilazapril 5mg and hydrochlorothiazide 12.5mg daily)*

Na+140 K+ 3.3 (but on a thiazide diuretic)

Aldosterone 846pmol/l, renin 7mu/l

Saline Suppression Test – aldosterone non-suppressible

CT adrenals – <u>normal</u>

<u>Diagnosis</u> – Primary aldosteronism – differentiate (radiologically inapparent) APA from BAH

Genetic Test for GRA

↓

Negative

↓

Bilateral adrenal vein sampling for aldosterone levels

↓

No lateralisation

↓

Diagnosis – Bilateral adrenal hyperplasia

↓

Treatment Medical (Aldosterone Antagonists)

↓

Weaned off existing antihypertensives and on to spironolactone

↓

BP now well controlled on Spironolactone 50mg daily (only)

Mr CN has a CT scan of his adrenal glands which reveals a 1.3cm diameter adenoma of the right adrenal gland.

Will a laparoscopic right adrenalectomy be curative???

Answer ..probably

Why the uncertainty???

We decided that in light of the relatively good size of the lesion and the clear radiological characteristics of an adenoma that we could avoid adrenal vein sampling

Mr CN's BP and hyperkalaemia were controlled with spironolactone and he went on to have a laparoscopic R. adrenalectomy

Antihypertensives stopped while in hospital (day 2 post-op)

Subsequently normotensive and normokalaemic on no treatment

17 year old boy (JP) from Glen Eden with extended family in Northland presents to ED with a minor sporting injury. BP noted to be 180/110. He is admitted and BP does not settle below 160/90. Auntie says there is a family history of high blood pressure and strokes on his father's side.

Na 144 K 3.1 urea 5 creatinine 80 venous bicarb 31

Renin < 3mU/L (low) Aldosterone 900 ug/l (high)

Saline suppression test - aldo. non-suppressible

CT – no adrenal mass or hyperplasia

↓

Genetic Test for GRA

↓

Positive

↓

BP initially controlled with low dose dexamethasone

↓

Later successfully converted to amiloride

Any other conditions mimicking primary aldosteronism which may cause diagnostic confusion???

62 year old woman with D2M for 12 years and hypertension for 10 years

Office BP 180/110

Today: Na 144 K 2.6 Bicarb 35 Cl 95

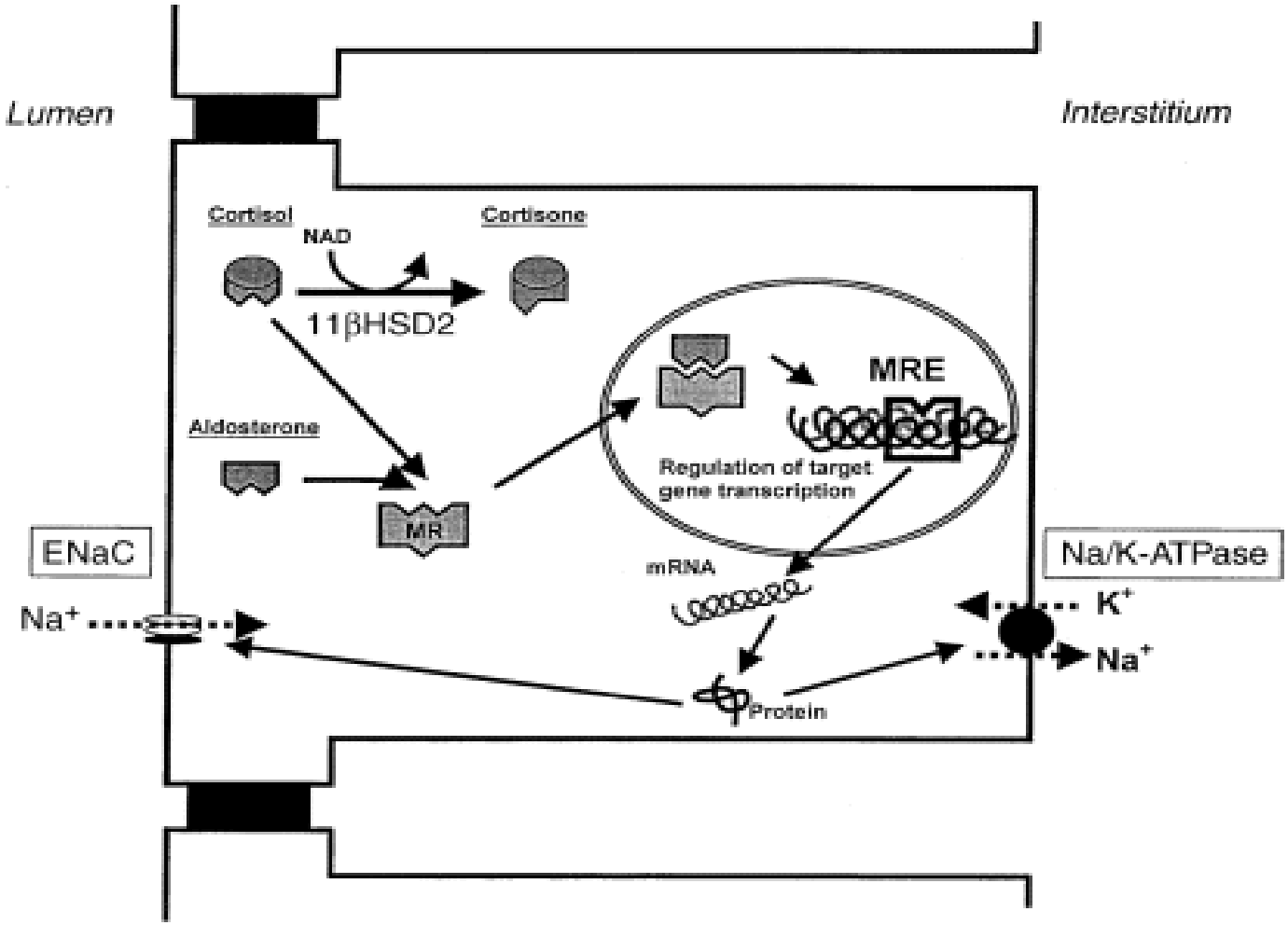
6 months ago: Na 138 K 4.5 Bicarb 26 Cl 101

Meds Candesartan, Frusemide, Verapamil, Vitamin E, Vitamin C, Ibuprofen, Herbal preparation

Renin 4mu/l (low) , aldosterone 95 pmol/l (low)

Clues – recent onset – therefore acquired rather than congenital

- data suggest the effect of a mineralocorticoid other than aldosterone


Lumen
Interstitium
Cortisol
NAD
Cortisone
11βHSD2
Aldosterone
MR
MRE
Regulation of target gene transcription
mRNA
ENaC
Na/K-ATPase
Na+
K+
Na+
Protein

Cortisol is present in many 100x concentrations of aldosterone and cortisol can bind the MR receptor (for which they have identical affinity) and overwhelm aldosterone – the reason it doesn't is that the enzyme 11 beta hydroxysteroid dehydrogenase 2 breaks cortisol in the cell down to cortisone and prevents it from interacting with minerallocortocoid receptors.

Glycyrrhizic Acid (Licorice) Blocks 11BHSD 2 which Increases access of cortisol to minerallocorticoid receptor causing sodium retention + potassium loss (mimicking the effects of excess aldosterone in Conn's Syndrome)

Apparent Mineralocorticoid Excess – acquired

Glycyrrhizic Acid (Licorice)

- Blocks 11BHSD 2
- Increases access of cortisol to minerallocorticoid receptor causing sodium retention + potassium loss

Glycyrrhizic Acid (50x sweeter than sugar) present in many herbal preparations to improve palatability, candies, medications, chewing tobaccos, teas, and present in 2/3 of Chinese herbal formulas

Monogenic Causes of Hypertension

- monogenic (single gene) forms of hypertension involve gain-of-function mutations that result in overproduction of minerallocorticoids, or increased minerallocorticoid activity

- clinical phenotypes include severe hypertension from birth, apparent volume expansion, suppression of plasma-renin activity and variable hypokalaemia

- Commonest is Glucocorticoid-Remediable Aldosteronism

- Congenital adrenal hyperplasia
- Glucocorticoid responsive hyperaldosteronism
- Apparent mineralocorticoid excess
  - Acquired
  - Hereditary
- Progesterone-induced hypertension (Activating MR Mutation)
- Liddle's Syndrome
- Gordon's Syndrome (PHA 2)
- Autosomal dominant hypertension with brachydactyly (chromosome 12)

(Mostly low aldosterone except GRA and CAH)