Diabetes and Endocrinology

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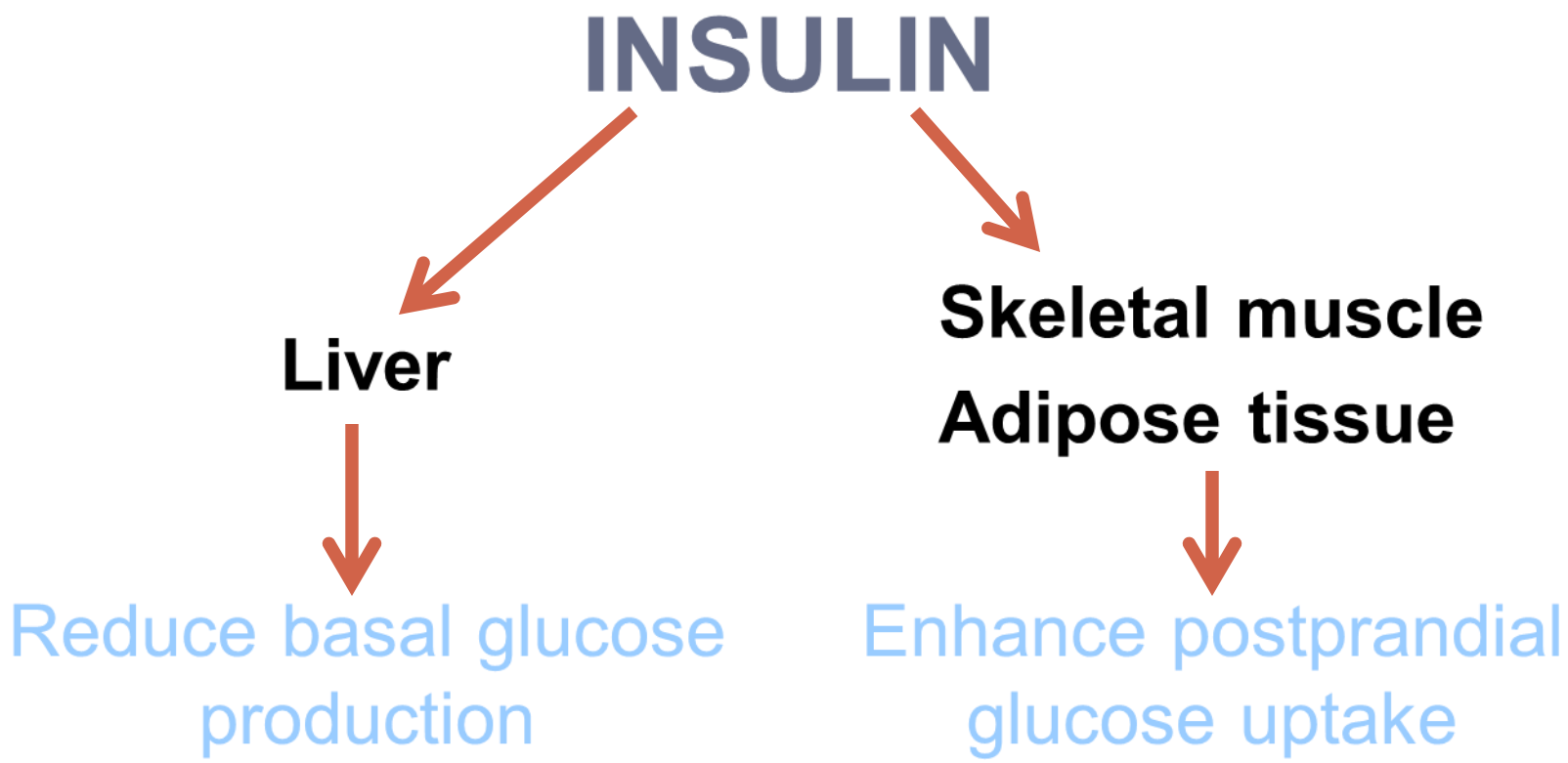
Diabetes

Failure of glucose homeostasis resulting from either:

- Lack of insulin secretion
- Failure of insulin effect

Insulin – Carbohydrate metabolism



Insulin – other effects

- Fat metabolism
  - PROMOTES Tg synthesis
  - INHIBITS Tg breakdown (FFA and KETONE BODIES)
- Protein metabolism
  - INHIBITS protein breakdown to AA (precursors for hepatic gluconeogenesis

Classification of Diabetes

- Type 1 Diabetes
  - B cell destruction
  - Immune mediated / Idiopathic
- Type 2 Diabetes
  - Insulin resistance
  - Relative insulin deficiency
- Gestational Diabetes
- Other
  - Diseases of the exocrine pancreatic disease
  - Genetic disease (B cell function, insulin action)
  - Endocrinopathies
  - Drugs

Type 1 Diabetes

Which of the following statements regarding Type 1 Diabetes is / are true

- T1DM results from the autoimmune destruction of α cells in the pancreas
- Patients typically need to reduce their insulin doses by 1/3 when ill
- Ketosis heralds insulin deficiency in the context of hyperglycaemia
- A variable rate insulin infusion is indicated in the acute management of diabetic ketoacidosis

Type 1 Diabetes

ABSOLUTE INSULIN DEFICIENCY

- Pancreatic β cell destruction
- Failure of insulin secretion

- Cardinal features:
  - Hyperglycaemia
  - Salt / water loss
  - Ketogenesis (uncontrolled breakdown of fat and muscle)

Therapeutic options in T1DM

.....Insulin

Therapeutic options in T1DM

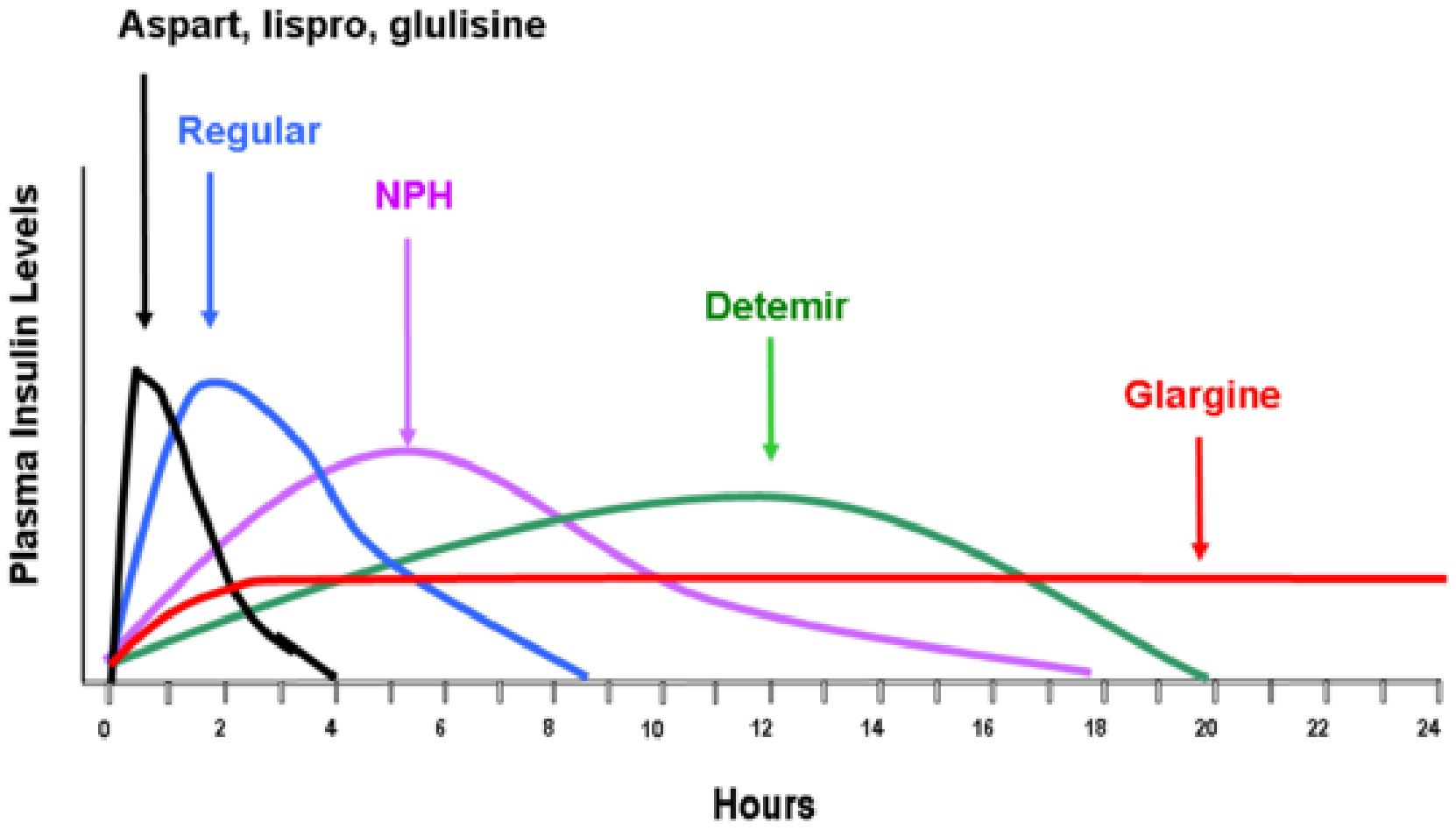
.....Insulin

....Or they die

Types of insulin

- Long acting
- Short acting
- Mixtures of the above

Insulin - Profiles of action



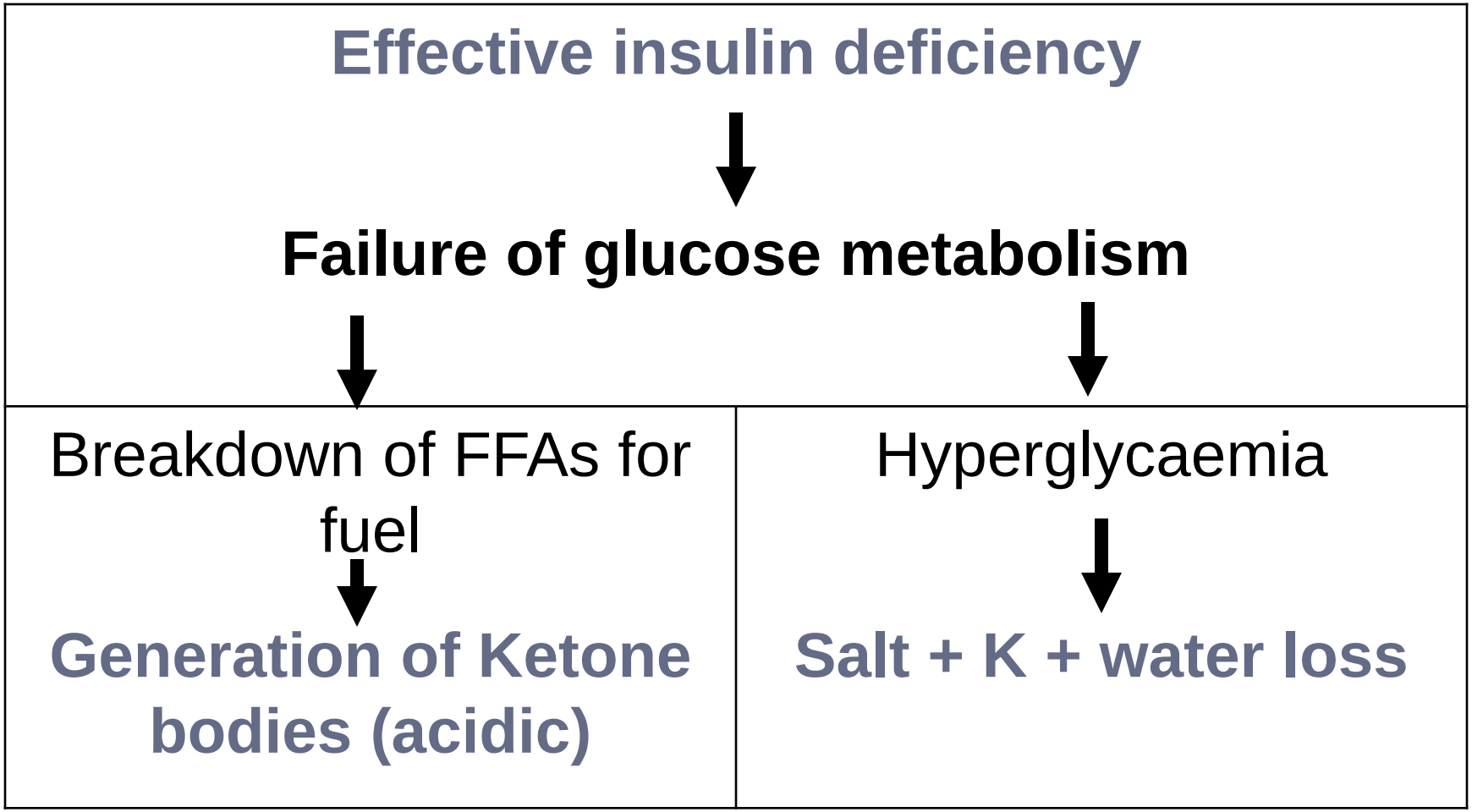
Continuous insulin infusion (“pumps”)

What are the features of insulin deficiency?

What are the features of insulin deficiency?

- **Ketosis**
- Salt, water, potassium loss (hyperglycaemic diuresis)
- Hyperglycaemia

What is ketoacidosis?



Diagnositc criteria - DKA

- Acidosis: pH < 7.3,
  HCO_3 < 15mmol/L,
  BE < -10

- Ketonuria ++ OR plasma ketones >3mmol/L

- Known diabetes OR plasma glucose >11mmol/L

Management – what are the priorities?

Management – what are the priorities?

- Restore salt and water
  - N Saline +/- K
- Replace insulin to terminate ketogenesis
  - Fixed rate insulin +/- 10% Dextrose

AVOID HYPOKALAEMIA

AVOID HYPOGLYCAEMIA

When can the fixed rate infusion stop?

As soon as ketogenesis is terminated

- Capillary ketone measurement <0.6mmol/l

- Surrogates:
  - Plasma HCO_3 (caution after 6hrs saline resuscitation)
  - Urine ketones - may remain positive for up to 24hrs following resolution of DKA
  - pH > 7.3

- If E+D return to basal bolus. If NBM covert to standard variable rate insulin infusion


S.S. FAT GUY

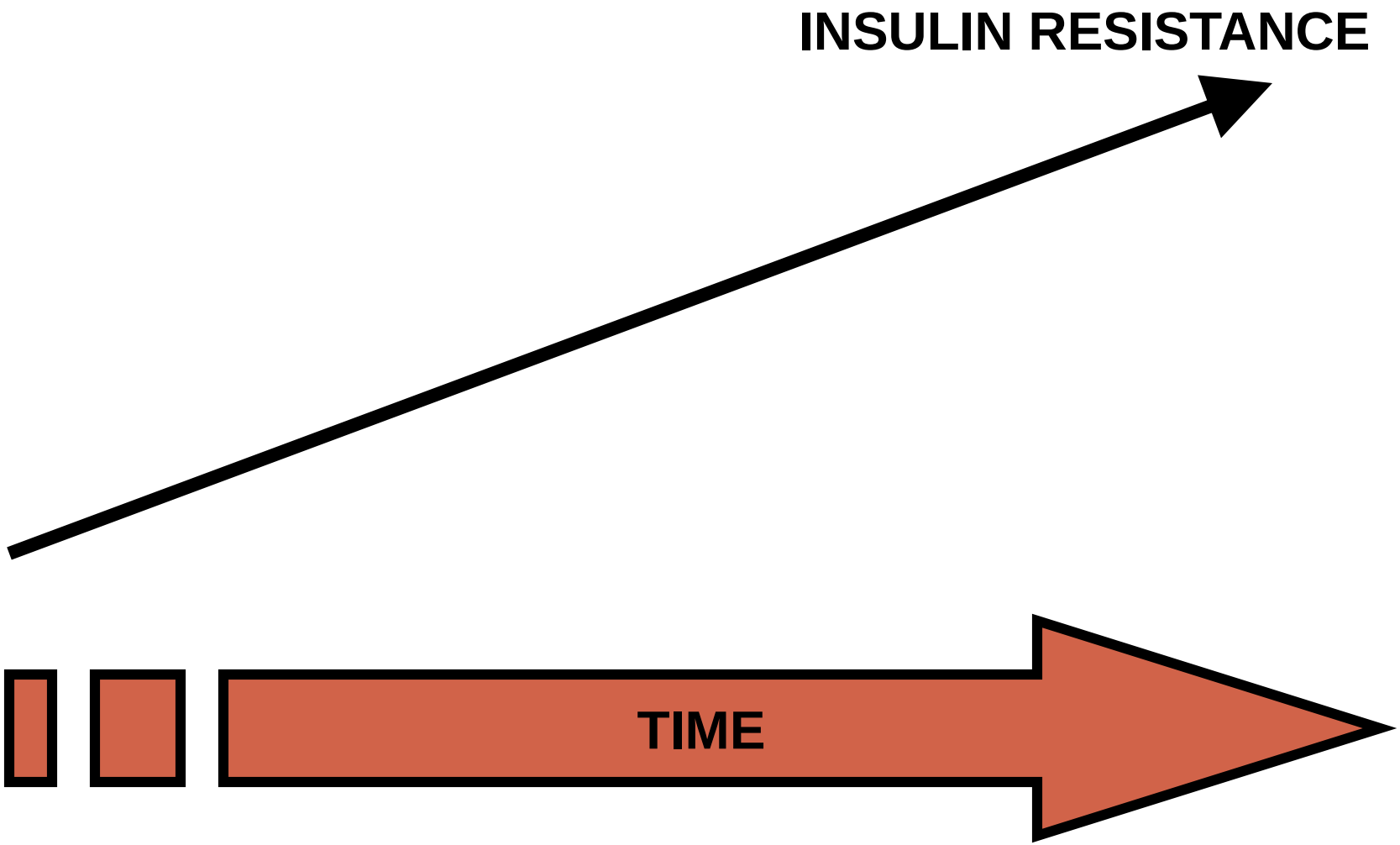
Type 2 Diabetes

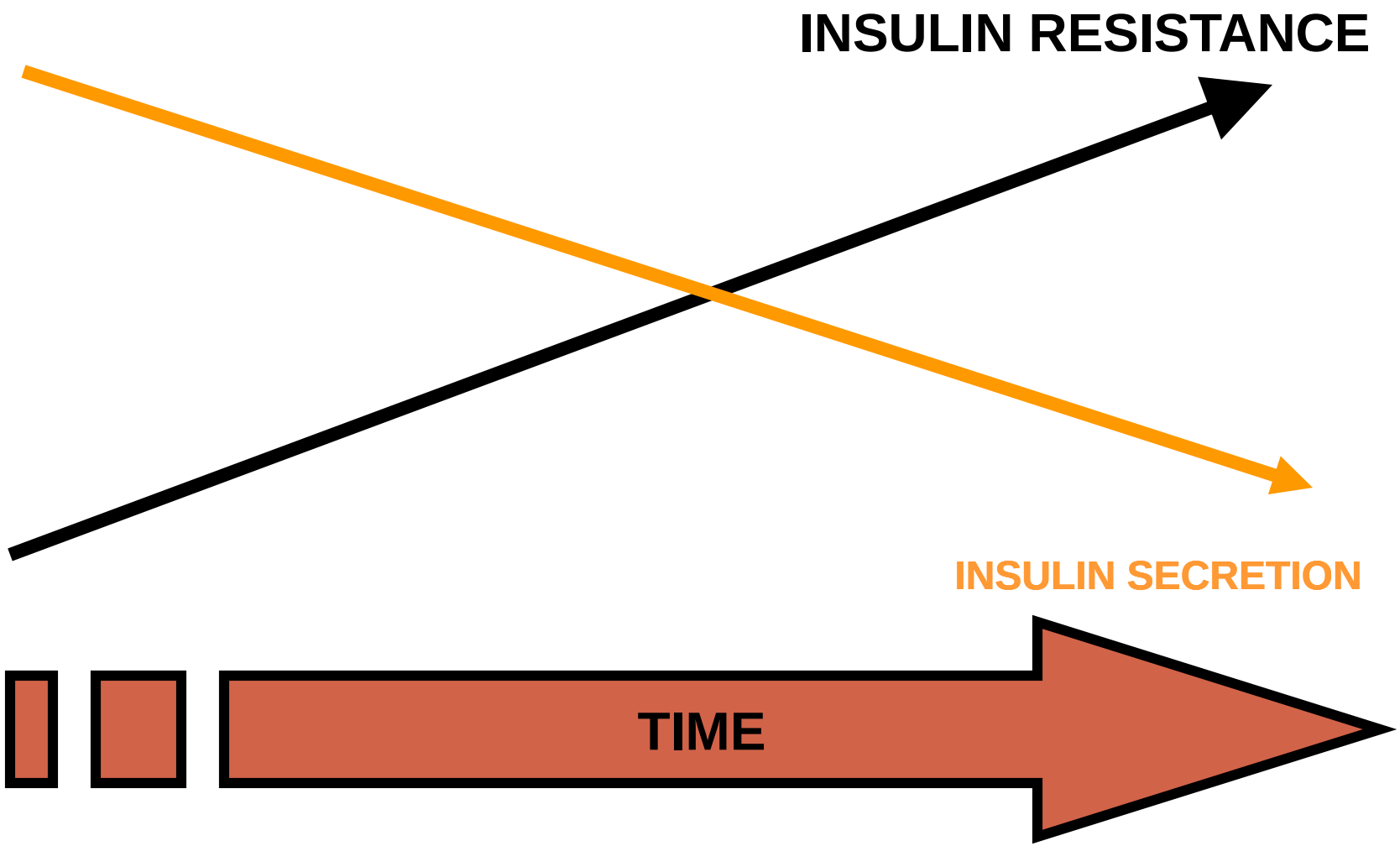
INSULIN RESISTANCE

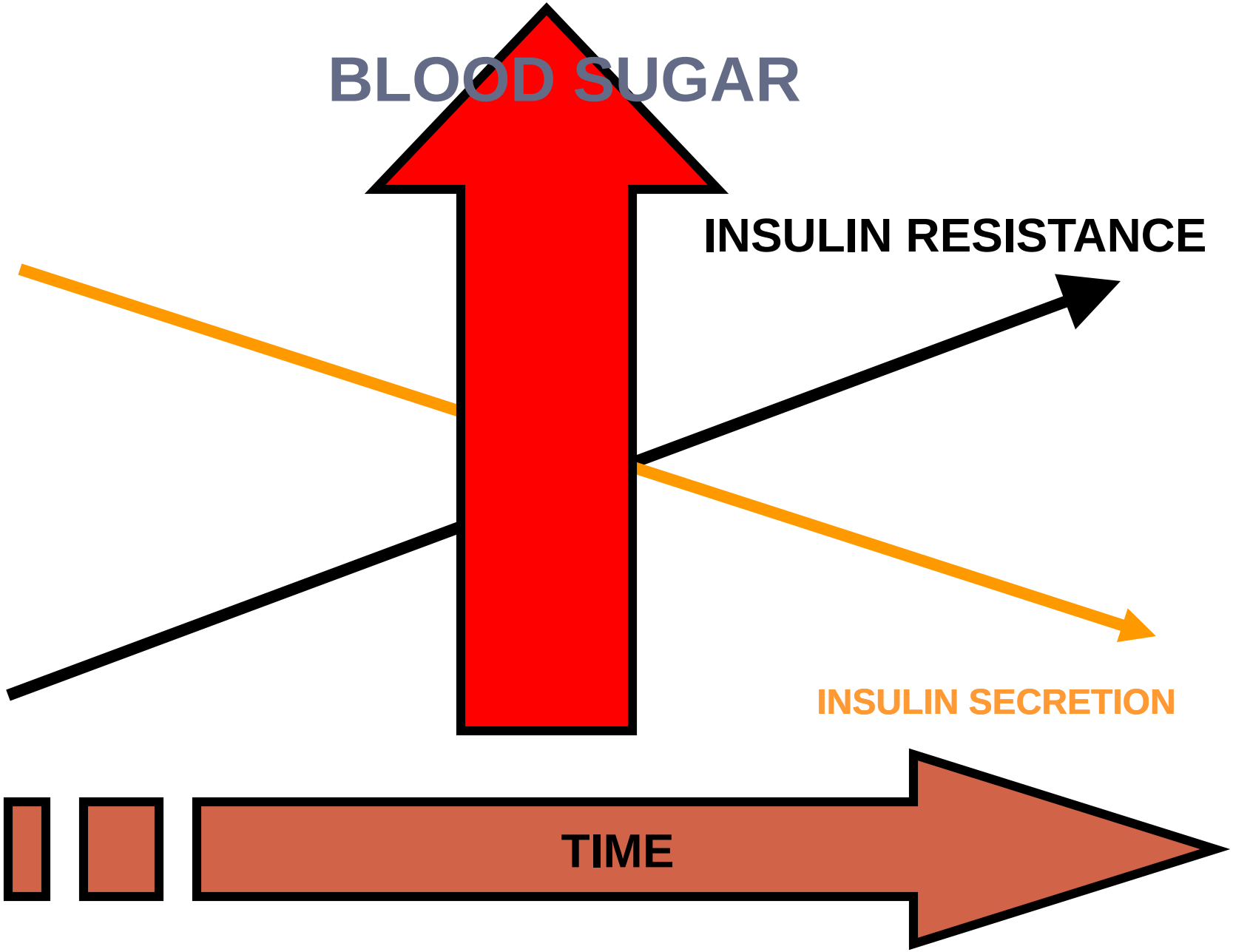
vs

Failing β cell function

= Relative insulin deficiency


INSULIN RESISTANCE
TIME


INSULIN RESISTANCE
INSULIN SECRETION
TIME


BLOOD SUGAR
INSULIN RESISTANCE
INSULIN SECRETION
TIME

Diagnosis

A 65 year old man describes symptoms of polyuria and polydipsia for 4 months. He has a family history of Type 2 Diabetes. His BMI is 32. Which of the following statements is true?

- An HbA1c measurement of 82mmol/mmol would confirm the diagnosis
- An HbA1c of 46mmol/mmol would exclude the diagnosis
- An OGTT is the only conclusive test for T2DM as recommended by the WHO
- Presence of Acanthosis Nigricans would support a diagnosis of Type 1 Diabetes
- Acromegaly is a recognised cause of insulin resistance

Diagnosis of Type 2 Diabetes

- HbA1c
  - Reflects glycaemia over 100 days
  - >48mmol/mmol
  - May be reduced by rapid RBC turnover eg anaemia
  - May be increased in certain ethnic groups
- OGTT
  - Fasting 7.1mmol/L
  - Two hr 11.1mmol/L
  - Not reliably reproducible

The different methods will detect slightly different populations

Secondary causes of Type 2 Diabetes

- Endocrinopathies
  - Cushing's Disease
  - Acromegaly
  - Phaeochromocytoma
  - Thyrotoxicosis
  - Glucagonoma
  - Somatostatinoma
- Drugs
  - Corticosteroids
  - Psychotropic drugs

..... Pregnancy (Gestational Diabetes)

Therapeutic options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Therapeutic Options

A 65 year old man attends his GP surgery with a history of T2DM diagnosed 6 months previously. He has managed to lose 5kg in weight with lifestyle changes and his HbA1c is 62mmol/mmol. His BMI is 30. Which of the following is true?

- His target HbA1c is 60mmol/mmol
- A good first line treatment for him would be a GLP1 inhibitor to help him lose more weight
- He should monitor his blood sugar levels to confirm fasting hyperglycaemia before commencing metformin
- A history of pancreatic cancer would be an absolute contraindication for offering him an SGLT2 inhibitor
- Presence of urinary ketones would be an indication for insulin therapy

Therapeutic options in T2DM

- Diet and exercise
- Insulin sensitiser
- Insulin secretagogue
- Reduce food absorption
- Increase glucose loss

- Insulin

Metformin

- Reduces hepatic glucose output
- Stimulates skeletal muscle glucose uptake

Side effects

- GI (Diarrhoea, bloating etc)

Contraindications

- Renal failure, heart failure, hepatic failure

FIRST LINE THERAPY

Thiazolidinediones

- “Glitazones”
- Reduce insulin resistance
- Work at the level of gene transcription – between 4 - 12 weeks for clinical effectiveness

Side effects

- Oedema, weight gain, osteoporosis

Suphonylureas

- Insulin secretagogues
- Will reduce blood glucose levels by 3 -4mmol/l
- Will reduce HbA_{1c} by 1.5 – 2%

Side effects

- Weight gain, risk of hypoglycaemia, particular caution in renal failure

Meglitinides

- Insulin secretagogues
- Glucose sensitive
- Short onset and duration of action

Side effects

- hypoglycaemia, URTI, headache

α Glucosidase inhibitors

- Acarbose
- Block the breakdown of complex carbohydrates in the small intestine

- Side effects
  - Flatulence, bloating

SGLT2 inhibitors

"Subtype 2 Sodium Glucose Transport protein inhibitors"

- Canagliflozin
- Dapagliflozin

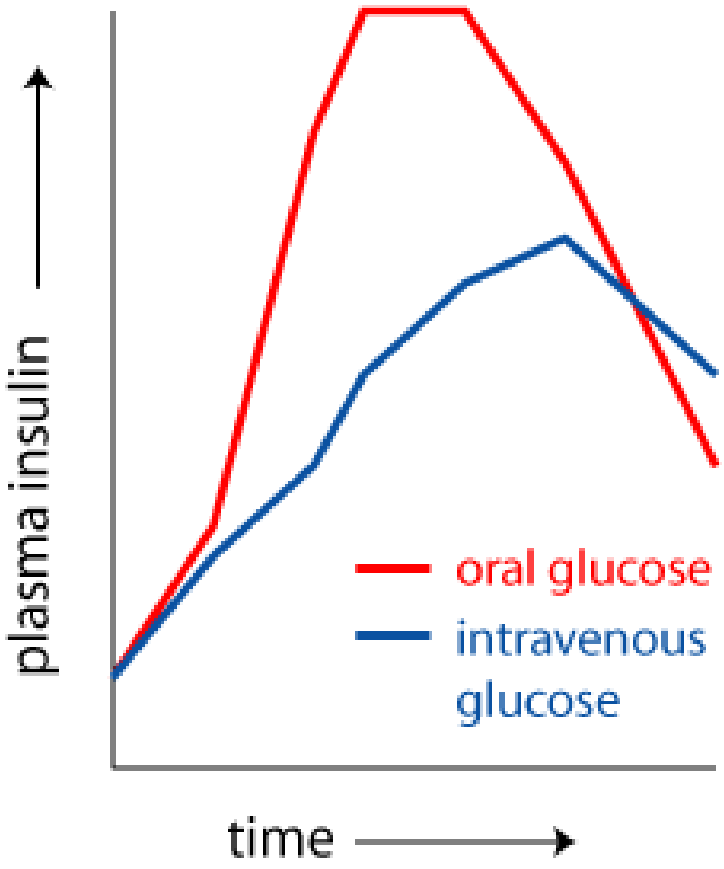
- Lower the renal threshold for glycosuria

Side effects:

- Vulvovaginal candidiasis
- **Postural hypotension (diuretic effect)**
- ?UTI
- ?bladder cancer

- Beware of glycosuria
- Limited risk of hypoglycaemia

The Incretin effect



Incretins

Enhance insulin release in response to a glucose load

- GIP: Glucose dependent insulinotropic peptide
- GLP1: Glucagon like peptide 1

....and increase satiety?

Extremely short half life of 2 minutes due to degradation by DPP IV

Therapeutic strategies with GLP1

- Longer acting GLP1 receptor agonists
  - Exenatide, Liraglutide
- DPP-IV inhibitors
  - Sitagliptin, Vildagliptin, Saxagliptin,

GLP1 receptor agonists

GLP1 receptor agonists

- Injectable (twice daily – once / week)
- Common side effects:
  - Nausea
- Limited risk of hypoglycaemia unless used in conjunction with insulin secretagogue
- ? Pancreatitis
- Safety warnings regarding pancreatic cancer / medullary thyroid cancer

DPP IV inhibitors “Gliptins”

- Oral medications
- Common side effects:
  - Headache, URTI
- Low risk of mild hypoglycaemia
- Perceived risk of pancreatitis, but unconfirmed
- Increase endogenous GLP1 levels
- Moderate effect on glycaemic levels, particularly early in the disease

Bariatric surgery

Restrictive procedures:

- Gastric band

Restrictive and malabsorptive procedures

- Gastric bypass

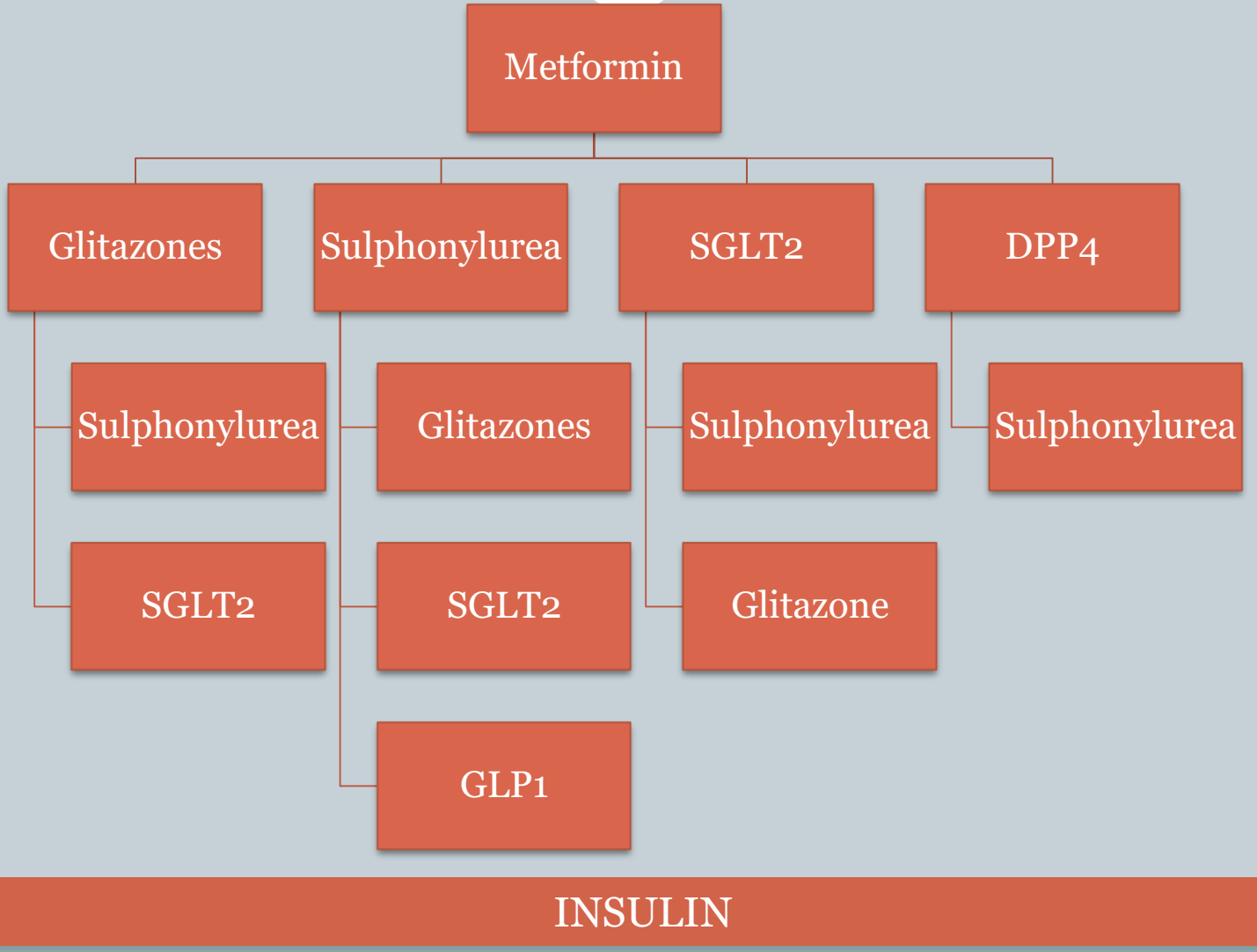
Significant weight loss can reverse diabetes

Therapeutic targets

Individually defined

- Aim to achieve HbA1c <48mmol/mmol if diet / lifestyle controlled +/- metformin
- Aim to achieve HbA1c < 53mmol/mmol if taking medications with risk of hypoglycaemia
- Intensify therapy where HbA1c <58mmol/mmol if individually appropriate

Therapeutic Pathways



Primary prevention measures

The GP notices that his blood pressure is 165/90mmHg despite adherence to lifestyle changes, Which of the following is correct?

- The optimal blood pressure would be 130/80mmHg
- A calcium channel blocker is a good first line agent
- In people of African / Caribbean origin dual therapy would be indicated as first line therapy combining an ACEI +/- Diuretic or Calcium Channel blocker
- Combining an ACEI and Angiotensin II receptor antagonist achieves optimal renal protection
- Antiplatelet therapy should be offered to all men aged >45 years

Primary Prevention

Blood pressure

- First line agent ACEI
  - African / Caribbean population ACEI + Diuretic or Calcium channel blocker
- Second / third line therapies
  - Diuretic / Calcium channel blocker

Antiplatelet therapy

- Not indicated as primary prevention

Hyperglycaemic Hyperosmolar State

HHS

(HONK)

Diagnosis

Hyperglycaemia

- typically blood glucose >30mmol/L

Hyperosmolar

- typically >340mOsm/kg

Ketones

- typically <+

Hyperglycaemic Hyperosmolar State (HHS)

- Hyperglycaemia
- Renal salt / water loss (dehydration)
  - Potassium wasting

Average fluid deficit 10-20L for 100kg man

Management….?

Management

- Restore circulating volume, gradually and safely … N Saline

Aim of treatment

Aim for a gentle but consistent fall in osmolality

Avoid tight control for 72 hours

(2 x Na + Glucose)

Why don’t we give insulin?

Long term complications of diabetes

Long term complications of diabetes

Microvascular

- Retinopathy
- Nephropathy
- Autonomic neuropathy
- Peripheral neuropathy

Macrovascular

- Atheromatous disease

The eye in diabetes

- Cataracts
- Reduced visual acuity due to osmotic changes
- Ocular nerve palsy
- Diabetic retinopathy
  - Thickening of the basement membrane
  - Increased vascular permeability
  - Aneurysm formation
  - Vascular occlusion

    =Ischaemia and growth of superficial fragile blood vessels

Nonproliferative retinopathy

- Microaneurysms
  - Weak points in the capillary wall leading to bulges
- Dot Blot Haemorrhages
  - Rupture of deeper microaneurysms
- Hard exudates
  - Leakage of serum proteins and lipids from weakened vessels
- Cotton wool spots
  - Nerve fibre infarction
- Venous beading and looping
  - Herald onset of neovascularisation

Proliferative retinopathy

- Growth of new vessels
- Haemorrhage
- Macular oedema

Endocrinology

…all you need to know about Endocrinology

- Pituitary disorders
- Thyroid disorders
- Parathyroid disorders
- Adrenal disorders
- Calcium homeostasis
- Endocrine emergencies

The Pituitary

Which of the following statements regarding pituitary macroadenomas is correct?

- May frequently be associated with low prolactin levels
- Typically associated with a homonymous hemianopia
- Larger size usually indicates malignancy
- May produce Growth Hormone, Gonadotrophins, Oxytocin
- May lead to CN III, IV and VI nerve palsy

Normal pituitary function

- Anterior pituitary hormones
  - ACTH
  - TSH
  - GH
  - Gonadotrophs (LH/FSH)
  - Prolactin (under inhibitory control)

- Posterior Pituitary Hormones
  - ADH (Vasopressin)
  - Oxytocin

NB Hypothalamic factors released via the posterior pituitary

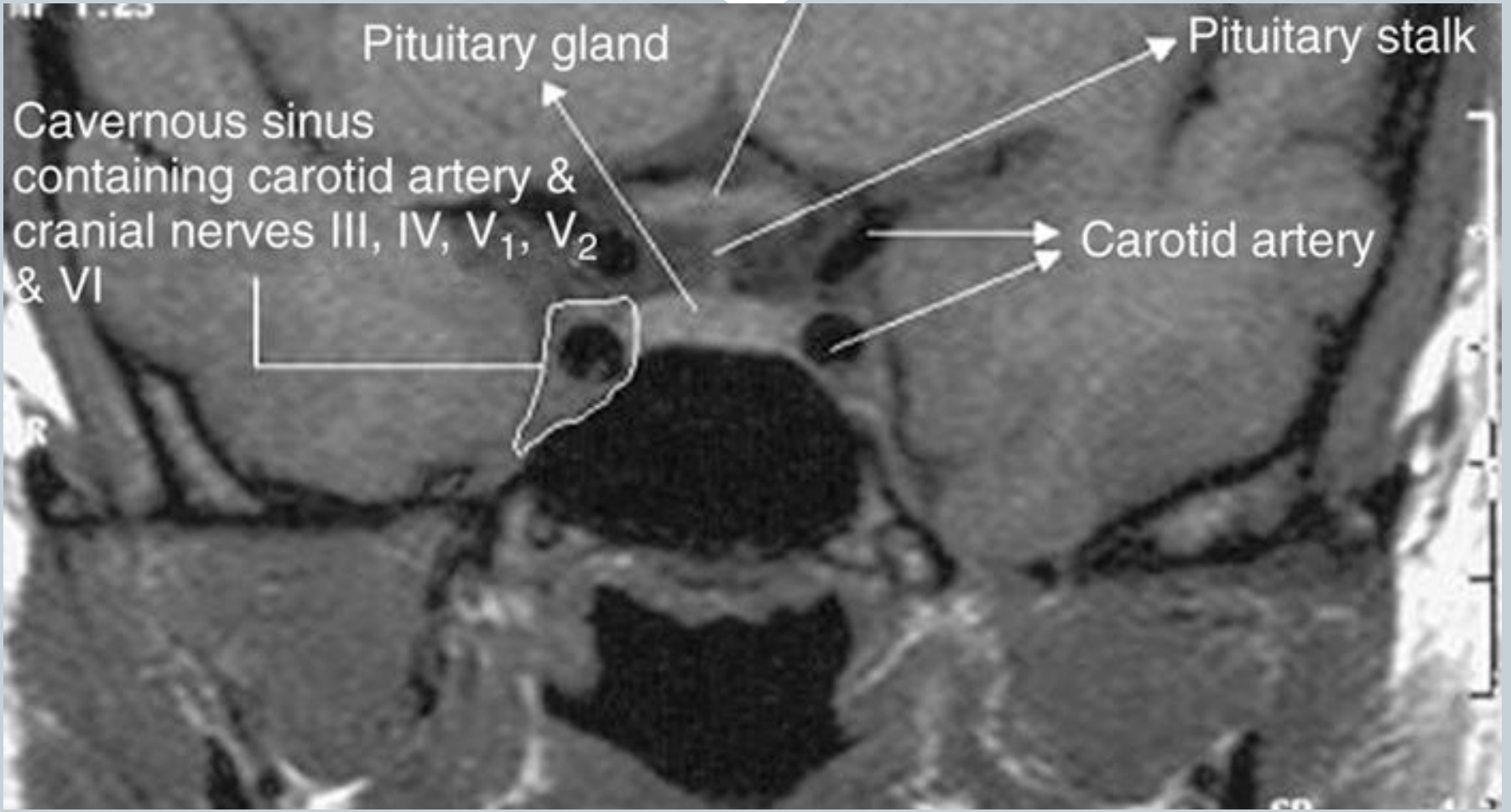
Disorders of the Pituitary

- Pituitary adenomas
  - Micro, Meso, Macroadenomas
  - Functioning / Non functioning
- Craniopharyngiomas
- Rathke's Cleft Cyst
- Inflammatory masses
- Infections
- Metastases
- (Primary malignancy)
- Empty Sella syndrome
- Trauma

Anterior Pituitary Tumours

- Local Compression
  - Failure of normal pituitary function
  - Bitemporal hemianopia
  - III, IV and VI palsy (V1, V2)
  - Loss of dopaminergic control and hyperprolactinaemia
  - Posterior pituitary function rarely affected
- Uncontrolled hormone release
  - ACTH – Cushing's Disease
  - GH – Acromegaly
  - LH / FSH – typically NFPA
  - Prolactin
  - TSH – (rare)

Anterior Pituitary tumours



Pituitary function tests

A 58 year old man is found to have a large pituitary adenoma after his optician detected a bitemporal hemianopia. Which of the following investigations would be appropriate in the **initial assessment** of pituitary function

- Midnight cortisol
- OGTT to stimulate Growth Hormone response
- TRH test
- Short synacthen test
- Water deprivation test

Pituitary function tests

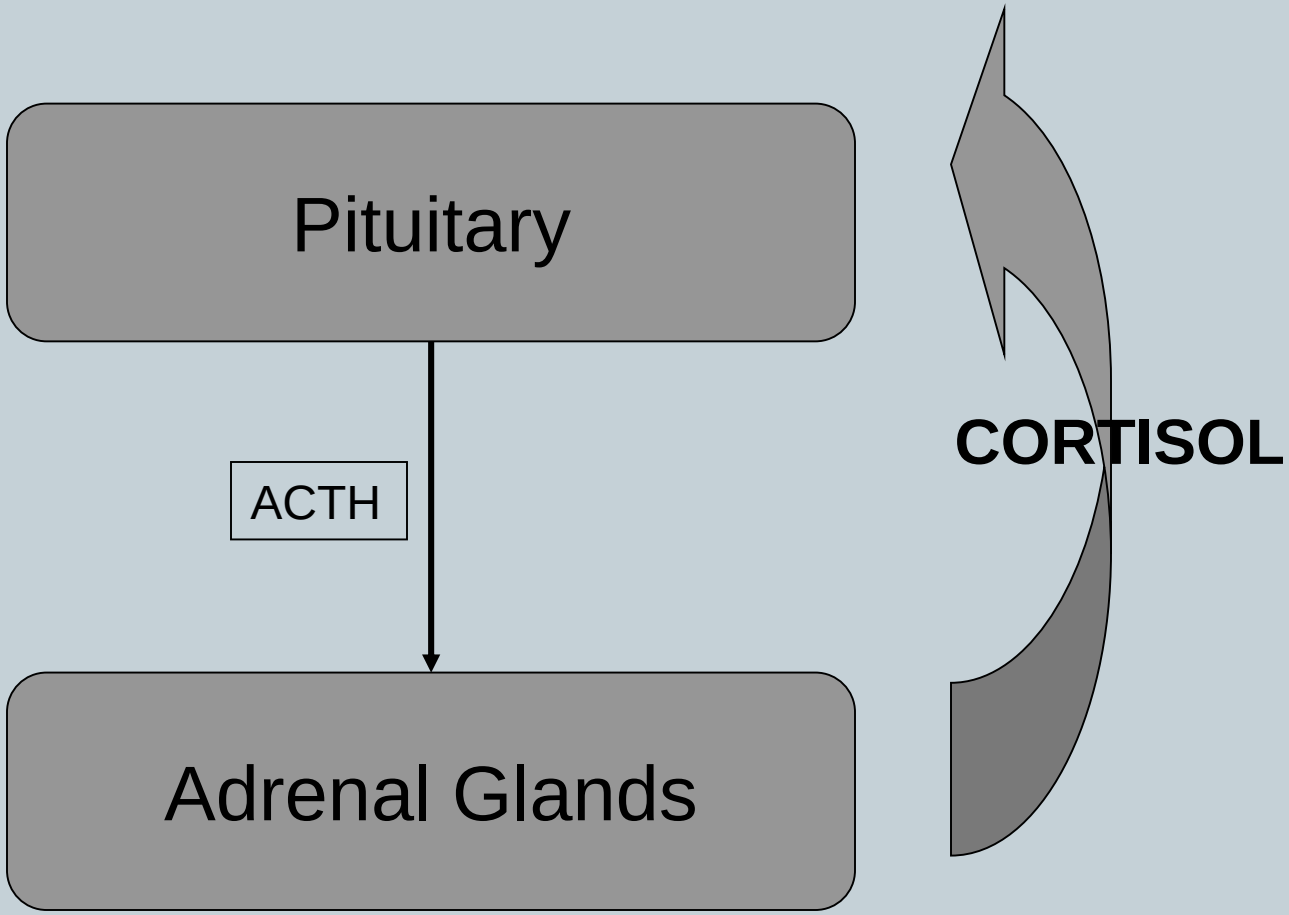
- Pituitary - adrenal axis
- Pituitary – thyroid axis
- Pituitary - gonadal axis
- Growth Hormone
- Prolactin

- Posterior pituitary function

Key points

- Most patterns of endocrine hormone secretion are diurnal / pulsatile
- Tests should be appropriately timed to assess for hypo / hyperfunction
- If it is too low – STIMULATE it
- If it is too high SUPPRESS it

Pituitary – Adrenal axis



Pituitary – Adrenal axis (tests)

ACTH / Cortisol deficiency:

ACTH / Cortisol excess:

Pituitary – Adrenal axis (tests)

ACTH / Cortisol deficiency:

- 0900 cortisol – Secretory peak (NB Shift workers)
- Insulin Tolerance Test / Glucagon test
- (Short SynthACTHen Test)

ACTH / Cortisol excess:

- MN cortisol – Secretory trough (NB Shift workers)
- LDDST
- HDDST

Insulin Tolerance Test (ITT)

Gold Standard test of pituitary - adrenal axis

- Iatrogenic induction of hypoglycaemia (<2.2mmol/l)
- Stimulates stress response
  - ACTH
  - GH

Glucagon test

- Causes transient rise then fall in blood glucose

Short synACTHen Test

- Many studies have shown good correlation with ITT in assessing both pituitary and adrenal function (Cortisol only)

Cushing's Syndrome

Which of the following statements is false, in the context of Cushing's Syndrome:

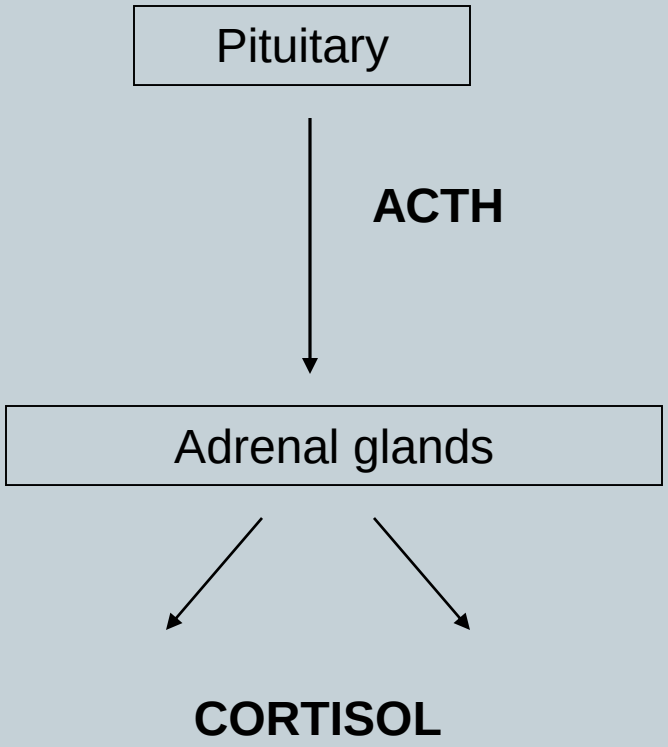
- Dexamethasone cross reacts with the biochemical assay for measuring serum cortisol
- Prednisolone cross reacts with the biochemical assay for measuring serum cortisol
- Abnormal cortisol dynamics can be associated with alcohol use
- A raised ACTH is diagnostic of pituitary dependent Cushing's Disease

Investigations in Cushing's Syndrome

- MN cortisol
- ACTH (Cushing's Disease, Ectopic ACTH)
- LDDST
  - 0.5mg dexamethasone every 6 hours for 48 hours
  - 1mg dexamethasone overnight
- HDDST
  - 2mg dexamethasone every 6 hours for 48 hours

What does it mean?

- Suppression on low dose = NORMAL
- Suppression on high dose = Pituitary driven cortisol excess through ACTH
- No suppression = Adrenal autonomy / ectopic ACTH



Gonadotrophins

A 36 year old man attends the clinic complaining of erectile dysfunction for one year. He completed normal puberty and has one child. His BMI is 42 and he was diagnosed with Type 2 Diabetes 5 years ago. Which of the following are true.

- Measured testosterone levels closely reflect biologically active “free testosterone”
- SHBG levels fall in chronic liver disease
- A diagnosis of Hypogonadotrophic Hypogonadism would be best treated with testosterone supplements
- Testosterone levels are highest at 4pm in the afternoon
- Testosterone therapy would help support spermatogenesis

Hyperprolactinaemia

A 36 year old lady complains of secondary amenorrhoea and galactorrhoea. Her prolactin levels are high. She is taking Risperidone. Which of the following statements is true?

- The presence of galactorrhoea excludes Risperidone as a cause for her symptoms
- Macroprolactinomas require urgent surgical reduction since they can grow unexpectedly
- Macroprolactin is a more severe form of hyperprolactinaemia seen when the levels are so high it starts to precipitate
- Prolactin levels can increase in response to phlebotomy
- Hyperprolactinaemia in men is usually associated with gynaecomastia

Hyperprolactinaemia

Aetiology:

- Failure of Dopaminergic suppression of prolactin release
  - Hypothalamic disorders
  - Drugs
  - Compression of pituitary stalk
- Lactotroph cell adenomas (Prolactinomas)
  - Micro / macro

Amenorrhoea, gallactorrhoea, local pressure effects

Hypopituitarism

Key **immediate** investigations

- Pituitary – adrenal axis
  - 0900 cortisol
- Pituitary – thyroid axis
  - TFT
- Prolactin
- Posterior pituitary function
  - Serum sodium, fluid balance (input/output), serum / urine osmolalities

Diabetes Insipidus

Which of the following options is NOT correct with regards to suspected Diabetes Insipidus

- Aggressive rehydration should be given with Normal Saline if hypotensive
- Lithium may be associated with nephrogenic diabetes insipidus
- Hypokalaemia is associated with tubular resistance to AVP
- In cranial diabetes insipidus the posterior pituitary bright spot may be lost

Diabetes Insipidus

Posterior pituitary

- Not typically associated with benign pituitary adenomas
- Uncontrolled inability to retain free water
- Polyuria with consequent polydipsia

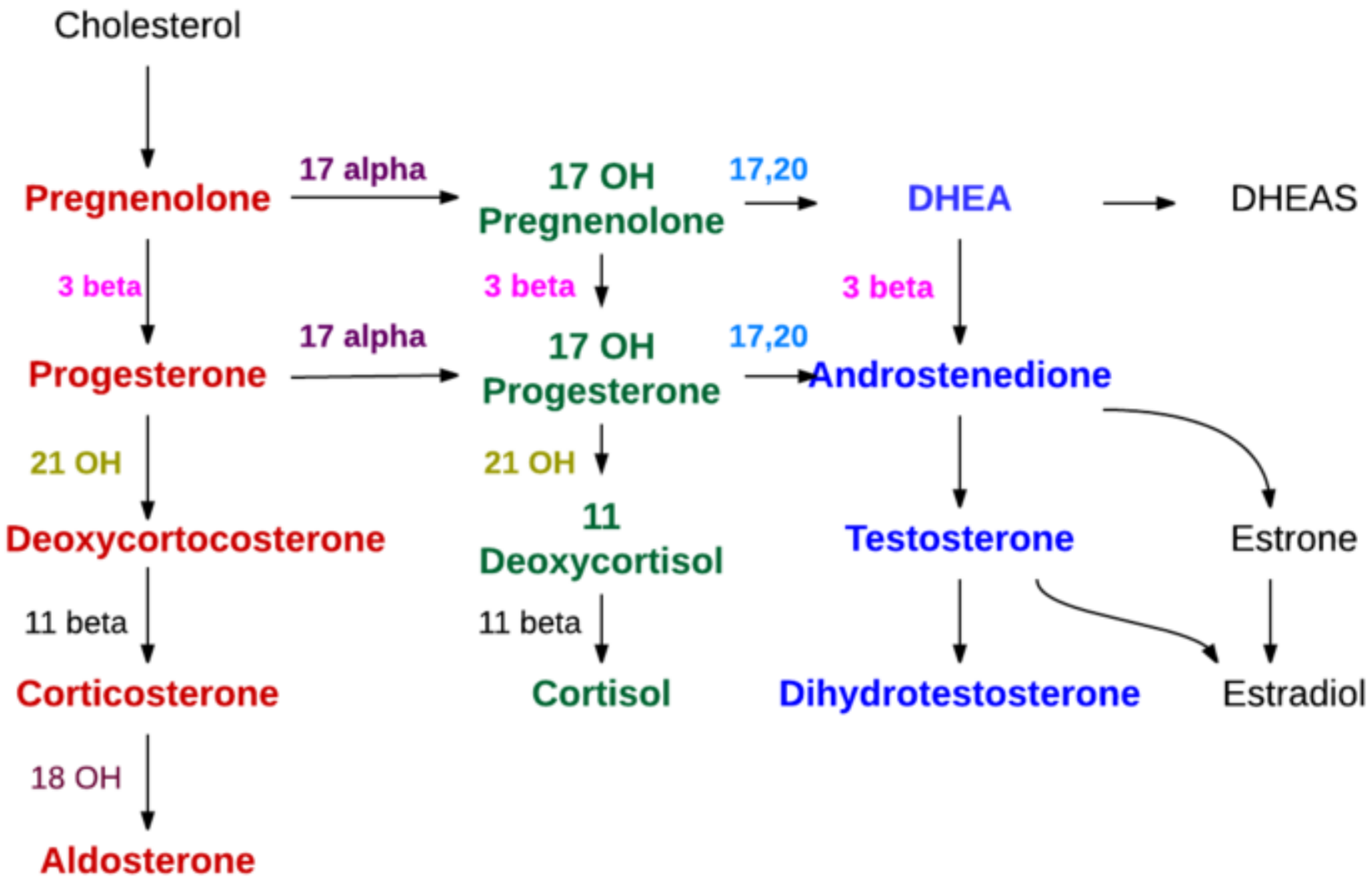
Investigations (ensure normal glucose / calcium levels)

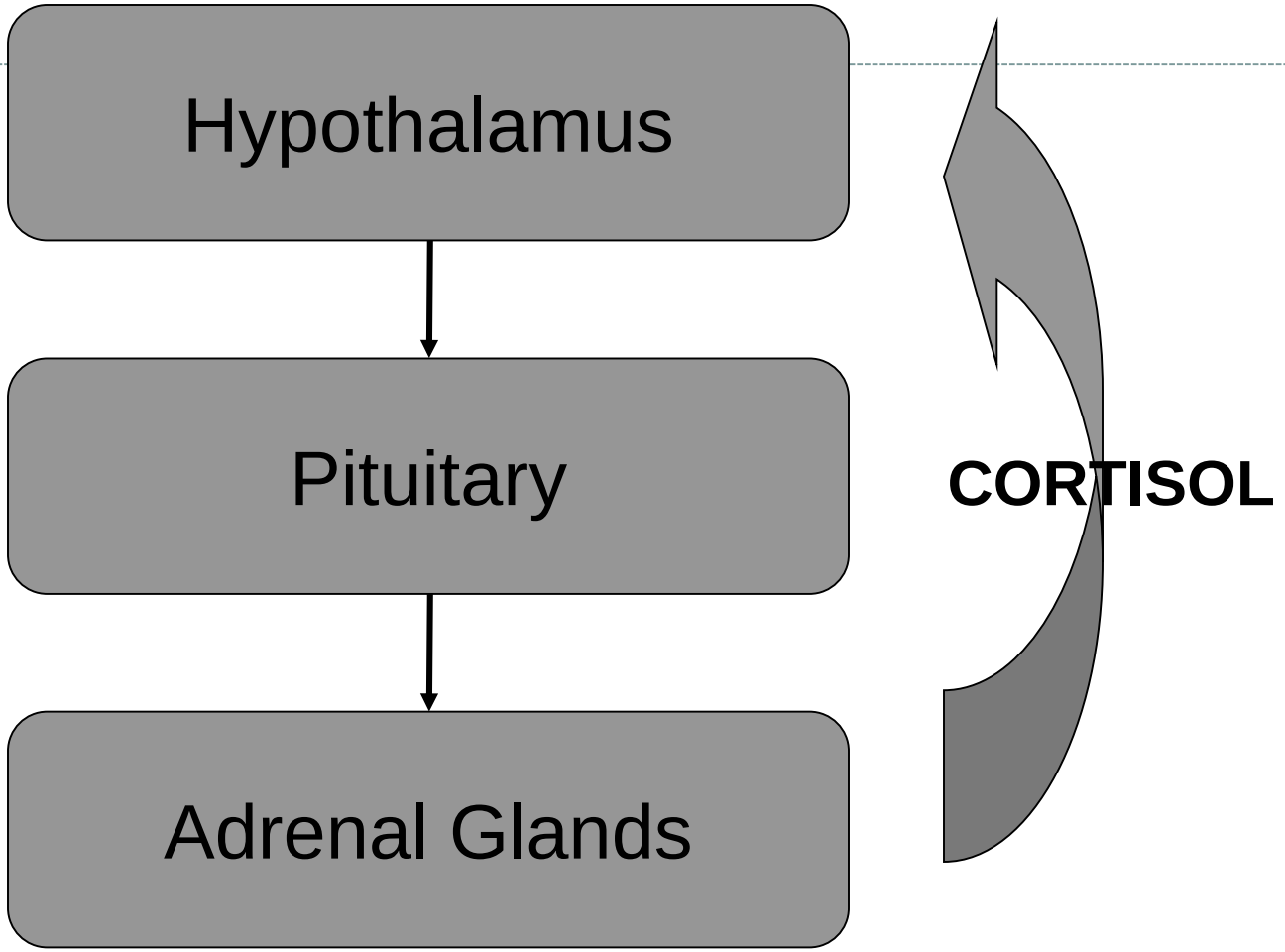
- Serum sodium
- Paired serum / urine osmolality
- Urine output
- (Water deprivation test +/- DDAVP)

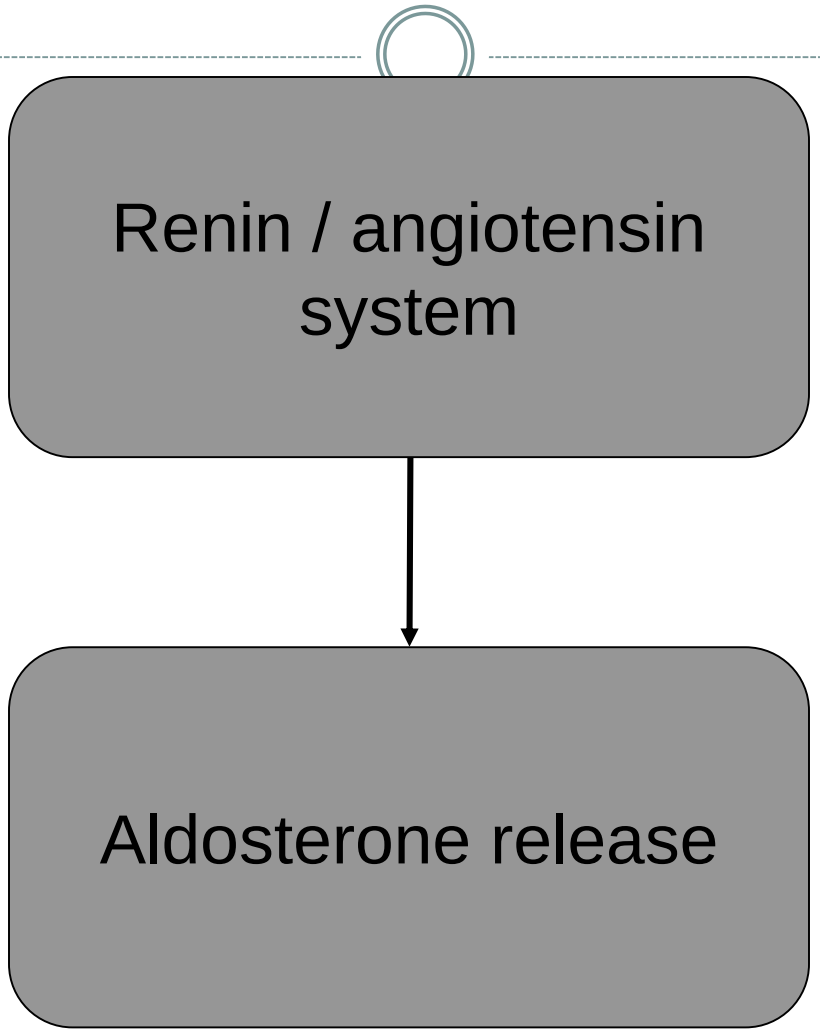
Hypoadrenalism

Adrenal cortex produces:

- Glucocorticoids (Cortisol)
  - Supports gluconeogenesis
  - Enhances vascular response to catecholamines
  - Varied other effects (anti-inflammatory etc)
- Mineralocorticoids (Aldosterone)
  - Sodium (+ water retention)
  - Maintenance of blood pressure
- Androgens / oestrogens


Cholesterol
Pregnenolone
17 alpha
17 OH Pregnenolone
17,20
DHEA
DHEAS
3 beta
3 beta
3 beta
Progesterone
17 alpha
17 OH Progesterone
17,20
Androstenedione
21 OH
21 OH
Deoxycortocosterone
11 Deoxycortisol
Testosterone
Estrone
11 beta
11 beta
Corticosterone
Cortisol
Dihydrotestosterone
Estradiol
18 OH
Aldosterone


Hypothalamus
Pituitary
Adrenal Glands
CORTISOL


Renin / angiotensin system
Aldosterone release

Hypoadrenalism

Primary

- Adrenal cortex not working (Loss of Cortisol and Aldosterone)
  - TB
  - Autoimmune destruction
  - Malignant infiltration
  - Adrenal infarction/haemorrhage
  - CAH

Secondary / Tertiary

- "Failure of higher control" (Loss of ACTH only)
  - **Cessation of longterm steroid tx (eg Prednisolone)
  - Pituitary/hypothalamic disease

Hypoadrenalism

True or False?

- In isolated ACTH deficiency there is relative protection from hyperkalaemia
- In isolated ACTH hypotension overwhelms the clinical presentation
- Normal saline is the rehydration fluid of choice
- It is important to wait for confirmation of low cortisol levels before replacing hydrocortisone in case the diagnosis is adrenal or pituitary TB

Primary adrenal failure

Loss of mineralocorticoid (aldosterone)

and

glucocorticoid (cortisol) effect

Effects of mineralocorticoid (aldosterone)deficiency overwhelm clinical presentation

Primary Adrenal Insufficiency

Loss of Aldosterone

Failure of salt / water retention

HYPOTENSION

Hyponatraemia

Hyperkalaemia

Metabolic acidosis

Presentation may be of insidious onset with abrupt decompensation due to intercurrent illness

Hyperpigmentation may be present reflecting high ACTH levels driving residual adrenal function

Secondary (tertiary) adrenal failure

Loss of glucocorticoid effect predominates (absence of ACTH drive to release cortisol)

- Loss of Cortisol reduces vascular responsiveness t o vasoconstrictive mechanisms
- Reduced gluconeogenesis
- Preserved AVP drives free water retention in the face of hypotension

NB patients on long term steroid tx

Secondary Adrenal Insufficiency

There may be evidence of previous steroid excess (exogenous), pituitary failure or pituitary tumour (visual field defect, cranial nerve deficit)

Loss of Cortisol

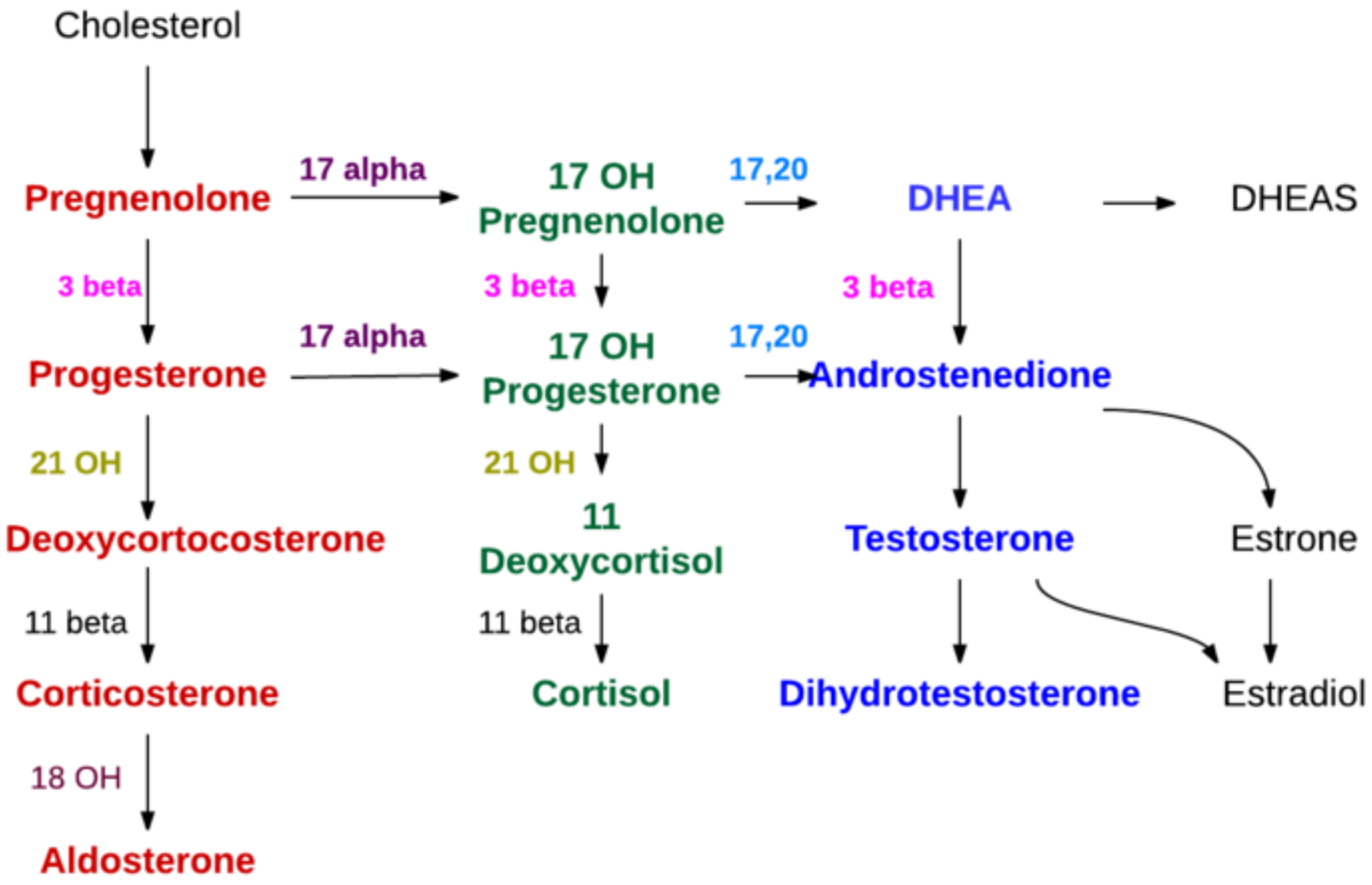
Hyponatraemia

Hypoglycaemia

Non Classical Congenital Adrenal Hyperplasia

Which of the following are features of late onset CAH

- Late onset CAH is an important differential in the diagnosis of PCOS in girls
- Late onset CAH in men is associated with early puberty
- Late onset CAH in men is associated with tall stature
- Late onset CAH in men may be associated with increased testicular size and high sperm count
- Late onset CAH is best diagnosed using a LDDST


Cholesterol
Pregnenolone
17 alpha
17 OH Pregnenolone
17,20
DHEA
DHEAS
3 beta
3 beta
3 beta
Progesterone
17 alpha
17 OH Progesterone
17,20
Androstenedione
21 OH
21 OH
Deoxycortocosterone
11 Deoxycortisol
Testosterone
Estrone
11 beta
11 beta
Corticosterone
Cortisol
Dihydrotestosterone
Estradiol
18 OH
Aldosterone

Thyrotoxicosis

Which of the following is pathognomic of Grave's Disease

- Lid lag
- Exophthalmos
- Tacchycardia
- Pretibial myoedema
- Diplopia

Aetiology

- Autoimmune thyrotoxicosis
- Toxic multinodular goitre
- Acute thyroiditis
- Amiodarone

- Homology with HCG (Hyperemesis Gravidarum)

Thyrotoxicosis

- Look for features of thyrotoxicosis (many mediated by the sympathetic nervous system)
- Consider specific features of autoimmune thyrotoxicosis (Grave's)
- Management:
  - Carbimazole, *Propylthiouricil
  - Propranolol
  - (*Steroids)
  - Radioactive Iodine
  - Surgery

*Reduce T4 to T3 conversion

Hypothyroidism (myxoedema coma)

Which of the following statements regarding hypothyroidism is / are true

- A low TSH and low Free T4 are diagnostic
- In suspected myxoedema coma it is important to replace thyroid function with sc T3 as an immediate priority
- Diastolic hypertension may be a feature and rewarming risks hypotension
- Mortality may be predicted in 20% cases

Hypercalcaemia

A lady is referred to the Endocrinology clinic with a PTH of 12.2pmol/L (NR 1.2-6.8). Which of the following statements may be true?

- A low vitamin D level may be associated with a high PTH
- Patients with confirmed hyperparathyroidism should not be offered vitamin D supplements incase this increases their serum calcium levels to dangerous levels
- Vitamin D deficiency results in reduced urinary calcium loss and may confound investigations for hypocalciuric hypercalcaemia
- Emergency management of hypercalcaemia includes intravenous Pamidronate with the patient on a monitored bed
- Bed rest is a recognised cause of hypercalcaemia

The End

THANK YOU
AND

GOOD LUCK