

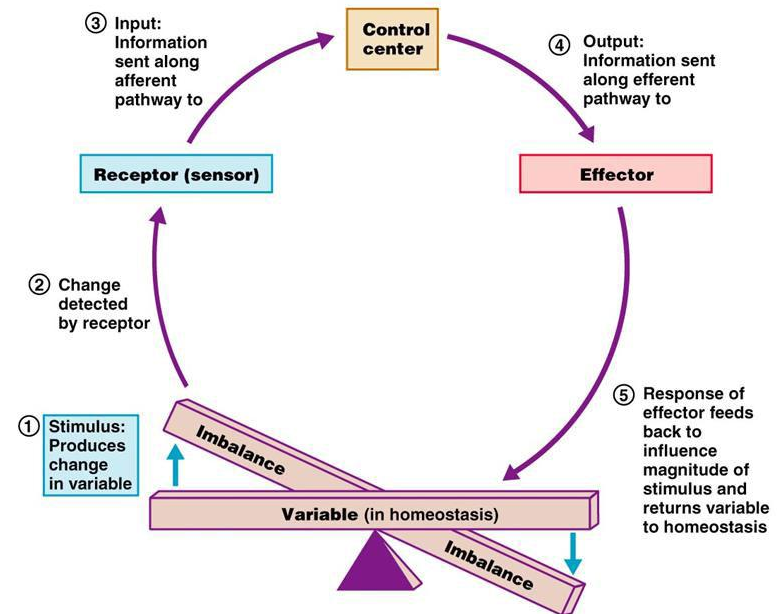
Learning Objectives

By the end of this session you will be able to discuss the pathology, diagnosis and treatment of the following diseases:

- Hyper- and hypothyroidism
- Cushing's disease
- Addison's disease
- Polycystic ovary syndrome
- Pineal gland

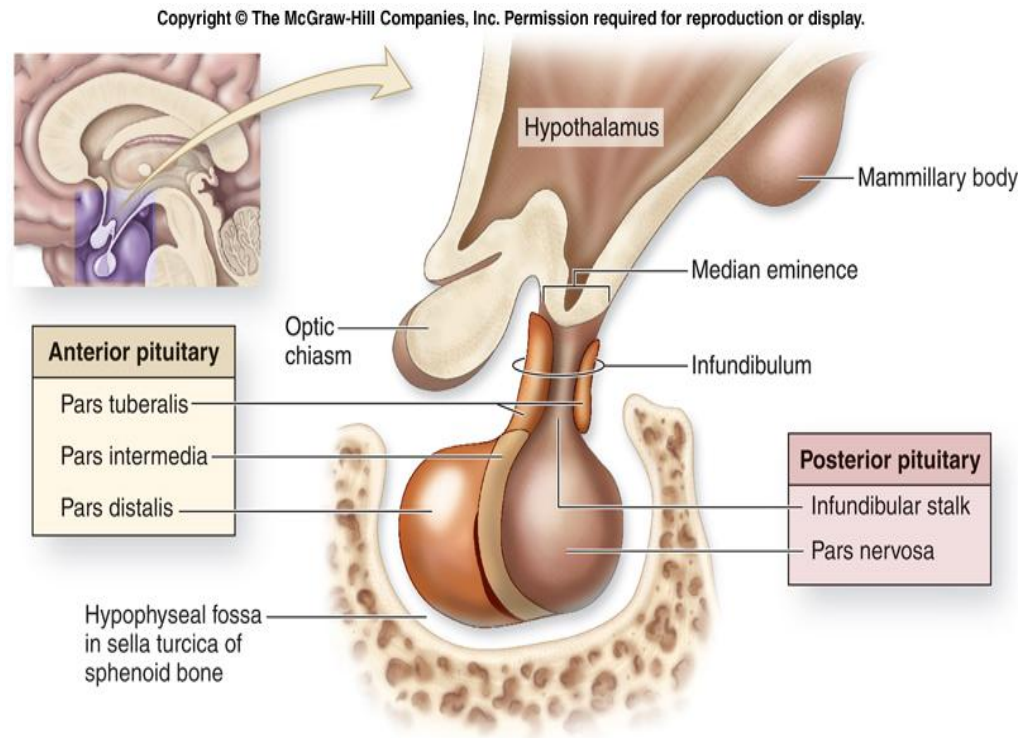
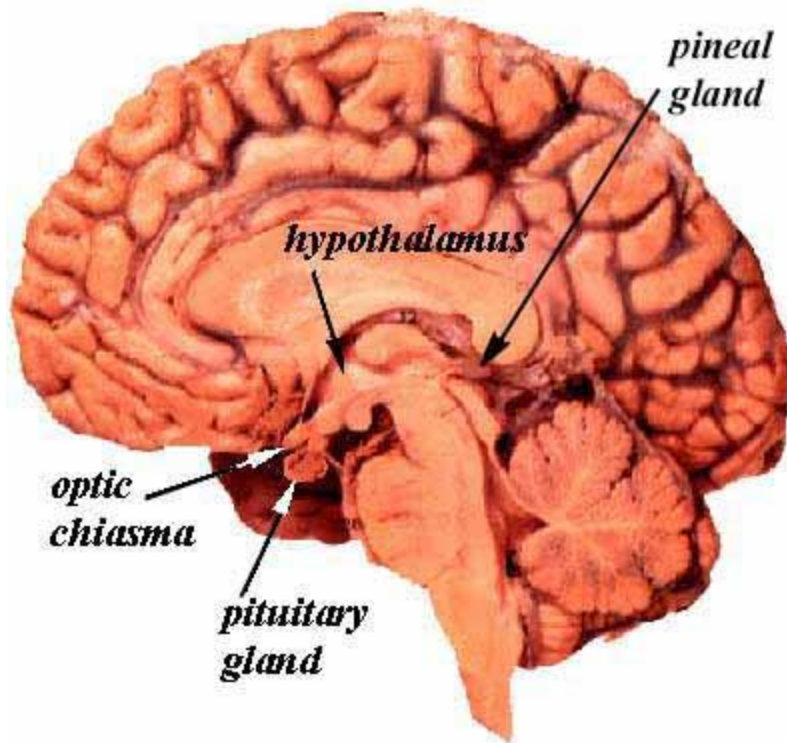
Endocrine Disease

- Endocrine disease is an imbalance of hormones
- They are based around too much or too little of the relevant hormone, with symptoms being an extreme version of normal effects



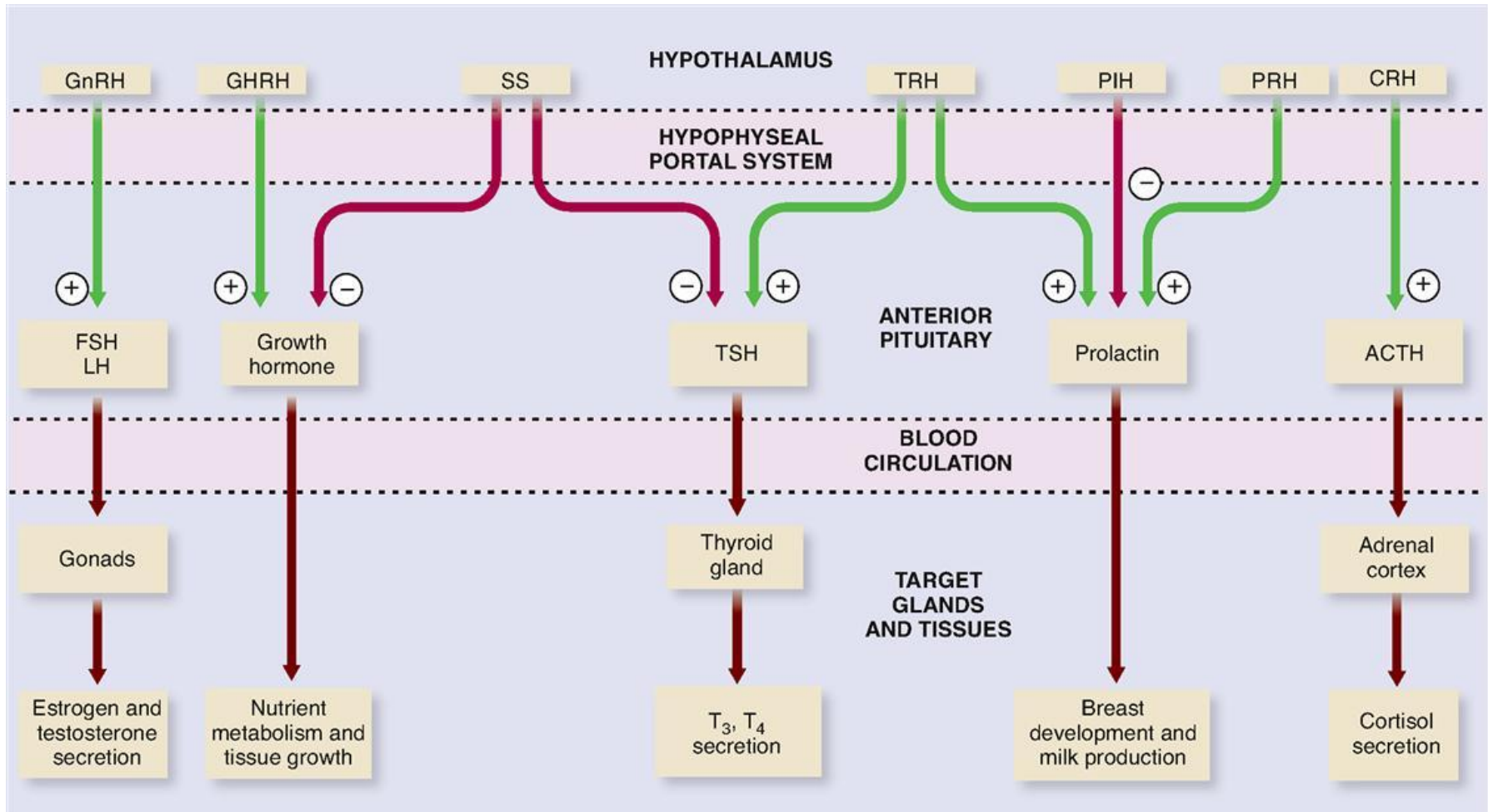
Pituitary Gland

The main gland involved in hormone control is the *anterior* pituitary gland

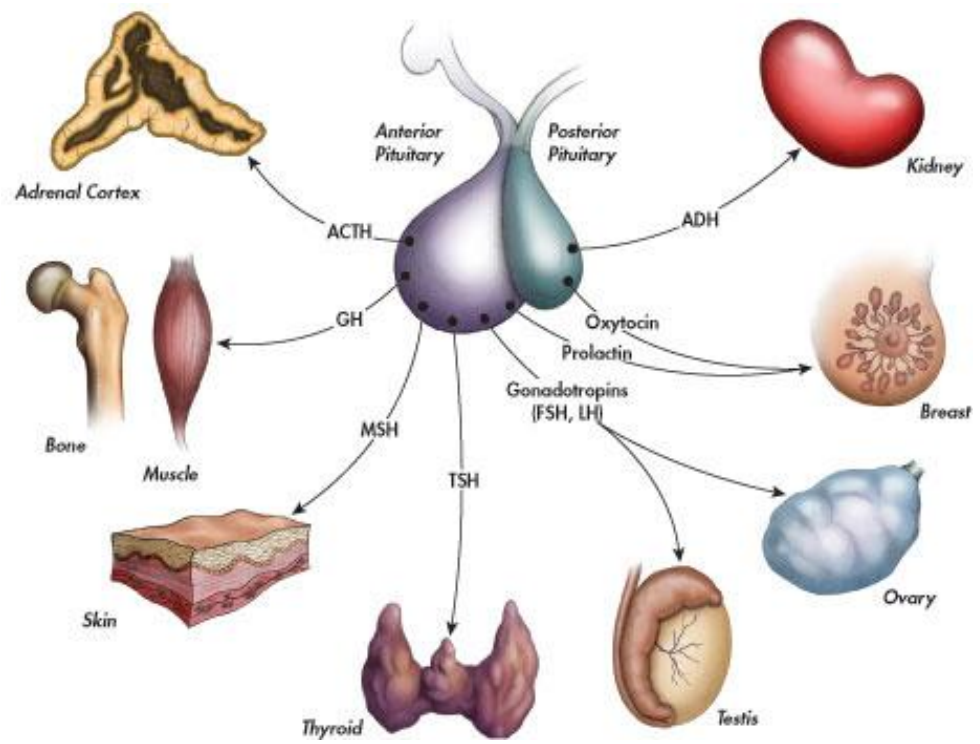
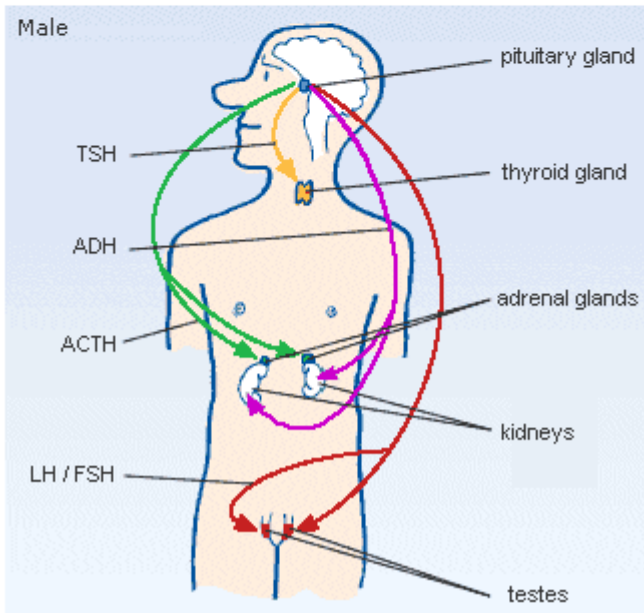
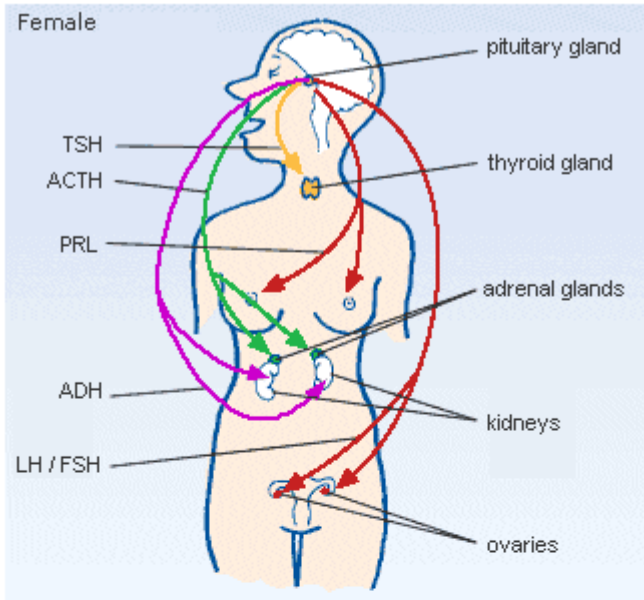


Now it's your turn.....

Link the hormones together to draw a picture of the feedback mechanisms related to the pituitary gland



Action of hypothalamic hormones. Hypothalamic hormones have releasing or inhibiting effects on the various cells of the anterior pituitary, thus regulating anterior pituitary secretion—and thus ultimately regulating the effects of anterior pituitary hormones throughout the body. *GnRH*, Gonadotropin-releasing hormone; *GHRH*, growth hormone–releasing hormone; *SS*, somatostatin; *TRH*, thyroid-releasing hormone; *PIH*, prolactin-inhibiting hormone; *PRH*, prolactin-releasing hormone; *CRH*, corticotropin-releasing hormone; *FSH*, follicle-stimulating hormone; *LH*, luteinizing hormone; *TSH*, thyroid-stimulating hormone; *ACTH*, adrenocorticotropic hormone; T_3 , triiodothyronine; T_4 , thyroxine. Ref: <https://basicmedicalkey.com/endocrine-glands/>

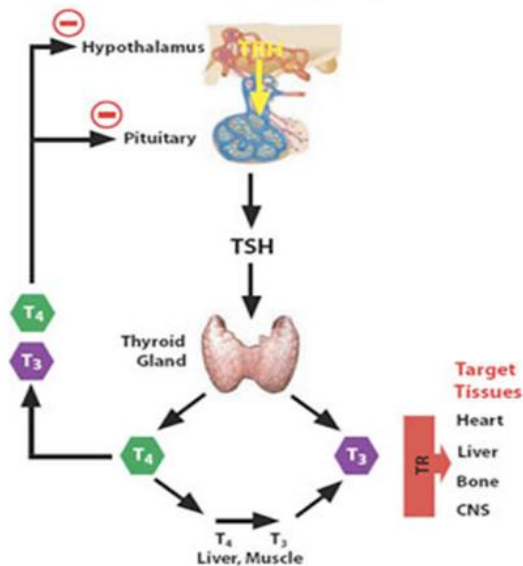


REMEMBER: All hormones are controlled by negative feedback

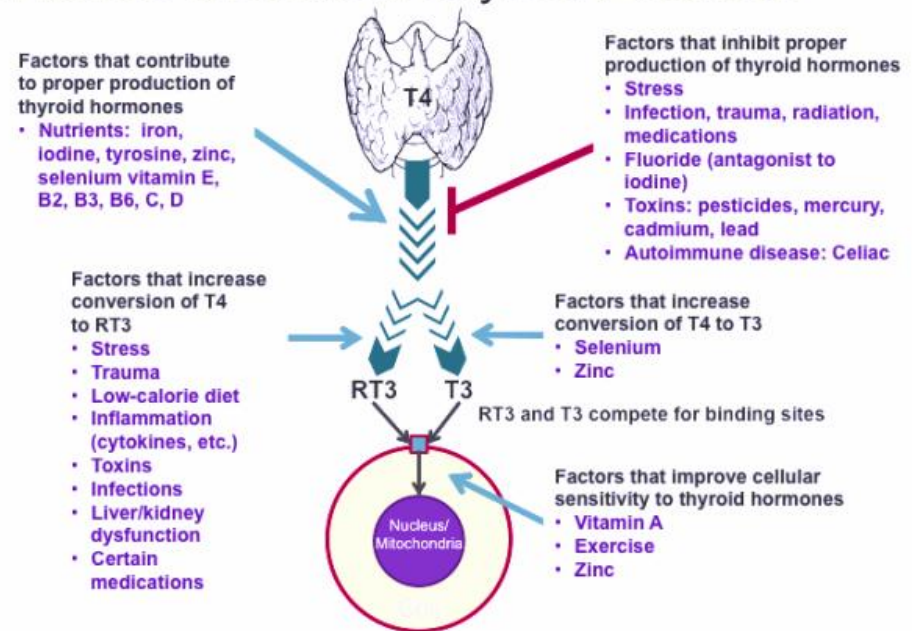
Thyroid Disease

- T4 is the main hormone produced by the thyroid gland.
- It is converted to T3 in target tissues
- T3 mediates the main actions of thyroid hormone, which include stimulation of cellular oxygen consumption and energy generation,

Hypothalamic-Pituitary-Thyroid Axis



Factors that Affect Thyroid Function



Thyroid Disease

- Hypothyroidism:
too **little** T3
- Symptoms include:
 - Fatigue
 - Weakness
 - Weight gain or increased difficulty losing weight
 - Coarse, dry hair
 - Dry, rough pale skin
 - Hair loss
 - Cold intolerance (you can't tolerate cold temperatures like those around you)
 - Muscle cramps and frequent muscle aches
- Hyperthyroidism:
too **much** T3
- Symptoms include:
 - Fatigue or muscle weakness
 - Hand tremors
 - Weight loss
 - Mood swings
 - Nervousness or anxiety
 - Rapid heartbeat
 - Heart palpitations or irregular heartbeat
 - Skin dryness
 - Trouble sleeping
 - Increased frequency of bowel movements
 - Light periods or skipping periods.

Thyroid Disease: Diagnosis

- Thyroid function tests - measurement of TSH, Free T3 and Free T4
- Hypothyroidism: Increased TSH, Low T3 and Low T4
- Hyperthyroidism: Decreased TSH, High T3 and High T4

Hypothyroidism: Treatment

- The dose of levothyroxine should be individualised
- The initial recommended dose is:
 - **For most people:** 50–100 micrograms once daily
 - Adjusted in increments of 25–50 micrograms every 3–4 weeks
 - The usual maintenance dose is 100–200 micrograms once daily.
- **For people aged over 50 years and people with cardiac disease or severe hypothyroidism:** 25 micrograms once **daily**, adjusted in increments of 25 micrograms every 4 weeks according to response.

Hypothyroidism: Monitoring

- Review the person every 3–4 weeks after initiation and adjust the dose accordingly, aiming to:
 - Resolve the symptoms and signs of hypothyroidism.
 - Normalise serum TSH and improve thyroid hormone concentrations to the euthyroid state.
 - Avoid overtreatment, especially in the elderly.
- Once a stable TSH is achieved, TSH can be checked 4–6 months and then annually.

Hyperthyroidism

- Hyperthyroidism occurs when an excess of circulating thyroid hormones is produced by an overactive thyroid gland.
 - Primary hyperthyroidism occurs when thyrotoxicosis is caused by an abnormality of the thyroid gland, such as in Graves' disease.
 - Secondary hyperthyroidism occurs when thyrotoxicosis is caused by abnormal stimulation of a normal thyroid gland, such as by a TSH-secreting pituitary tumour.

Hyperthyroidism: Treatment

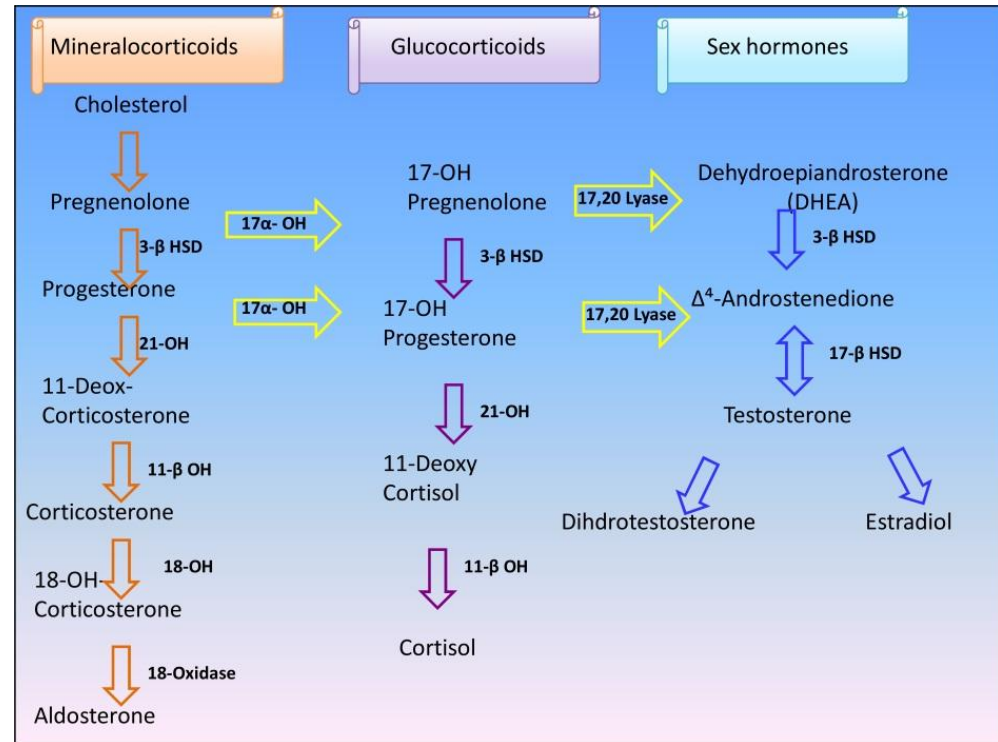
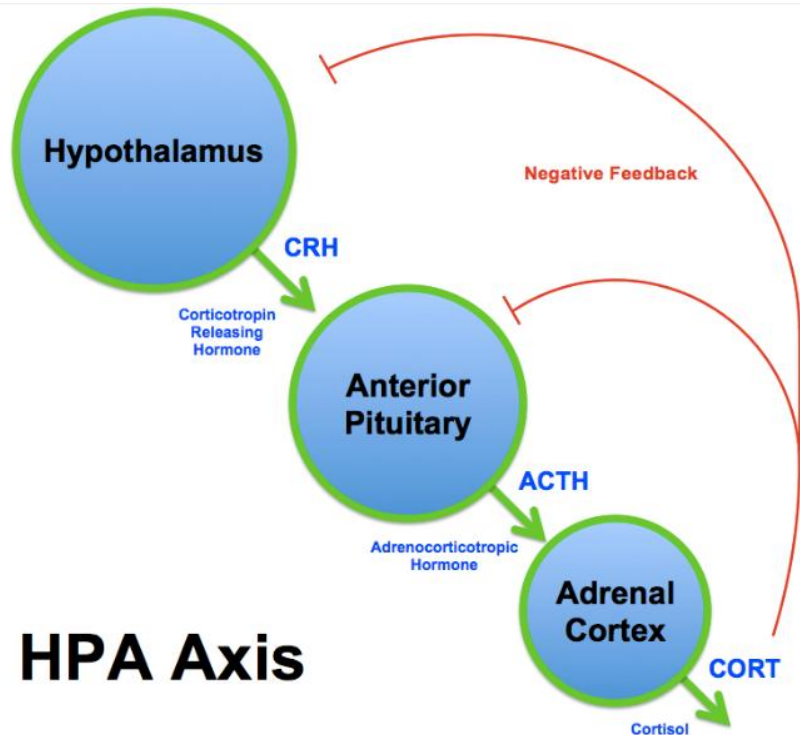
- Antithyroid drug treatments (carbimazole and propylthiouracil) are used to decrease thyroid hormone synthesis
- Only initiated on specialist advice:
 - Short-term in preparation for radioiodine treatment or surgery.
 - Medium-term with the aim of inducing remission of Graves' disease.
 - Long-term where radioiodine treatment or surgery is contraindicated or declined.
- Propylthiouracil is usually second-line, due to a small risk of severe liver injury (about 1 in 10,000 adults), except in certain circumstances such as in the first trimester of pregnancy, or for treatment of thyroid storm.

Hyperthyroidism: Treatment

- After euthyroidism is achieved, two different treatment regimes may be used, which require regular blood monitoring
 - Titration-block regime
 - Block and replace regime
- For both regimes, the remission rate is about 50% if treatment is continued for 6–18 months and then stopped

Adrenal Disease

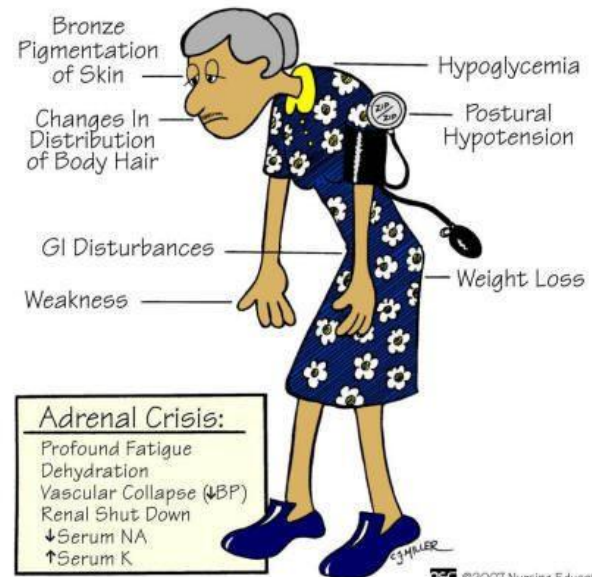
- The adrenal glands are responsible for production of three major hormone groups



Addison's Disease

- Addison's disease (primary adrenal insufficiency) is caused by destruction of the adrenal cortex usually from autoimmune disease.
- Symptoms are persistent but non-specific such as:
 - Fatigue
 - Hyperpigmentation
 - gastrointestinal symptoms
 - Cravings for salt, soy sauce, or liquorice
 - Musculoskeletal symptoms
 - Postural dizziness due to hypotension

ADDISON'S DISEASE



Addison's Disease: Diagnosis

- If Addison's is suspected, then a serum cortisol level and urea and electrolytes should be checked.
- The serum cortisol level should ideally be obtained at 8–9 am. Random serum cortisol levels have a low sensitivity for Addison's disease due to diurnal variation
- Sodium levels may be low and potassium levels high in Addison's disease (mineralocorticoid effect).
- As a general guide, if the serum cortisol level is:
 - < 100 nanomol/L adrenal insufficiency is highly likely
 - 100–500 nanomol/L, refer the person to an endocrinologist for further investigations, including an adrenocorticotrophic hormone stimulation (Synacthen) test

- The diagnosis of Addison's disease is usually confirmed in secondary care.
- For the adrenocorticotrophic hormone (ACTH) stimulation (Synacthen[®]) test:
 - Check serum cortisol levels before and 30 minutes after administering 250 micrograms of tetracosactide (a synthetic analogue of ACTH) intravenously or intramuscularly.
 - Performed at any time of day
 - A normal response to the ACTH stimulation test is an increase in the serum cortisol level.
 - In people with normal adrenal reserve, cortisol levels increase to more than 500–550 nanomol/L after 30 or 60 minutes.
 - In people with adrenal insufficiency, serum cortisol levels do not increase adequately because the adrenal cortex is already receiving maximum stimulation from endogenous ACTH.

Addison's Disease: Treatment

- Treatment for Addison's disease is usually initiated and adjusted by a specialist endocrinologist, but repeat prescriptions may be provided in primary care under a shared care arrangement.
- Hydrocortisone is used for glucocorticoid replacement, but longer-acting glucocorticoids, such as prednisolone and dexamethasone are sometimes used
 - The dose is usually 15–30 mg in divided doses (depends on body weight, metabolism, and absorption)
 - Fludrocortisone is used for mineralocorticoid replacement
 - Dehydroepiandrosterone (unlicensed) may be prescribed by some specialists for androgen replacement
 - Not all patients require mineralocorticoid or androgen replacement

Adrenal Crisis

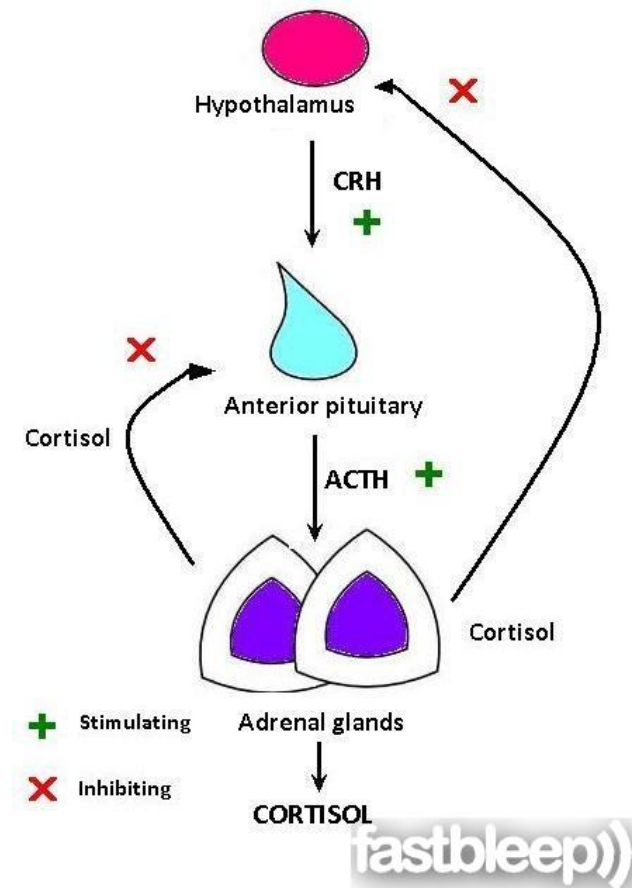
- The most serious complication of Addison's disease is adrenal crisis, often as a result of severe physical stress.
- The adrenal glands cannot supply the extra corticosteroids needed to cope and life-threatening symptoms develop
- Adrenal crisis may precipitate severe dehydration, hypotension, hypovolaemic shock, altered consciousness, seizures, stroke, or cardiac arrest
- Immediate 100mg hydrocortisone IM should be given by the patient or carer if symptoms develop and sent to hospital immediately
- Hydrocortisone 100 mg IV QDS is given, alongside aggressive fluid replacement and treatment of hyperkalemia

Self Care Advice

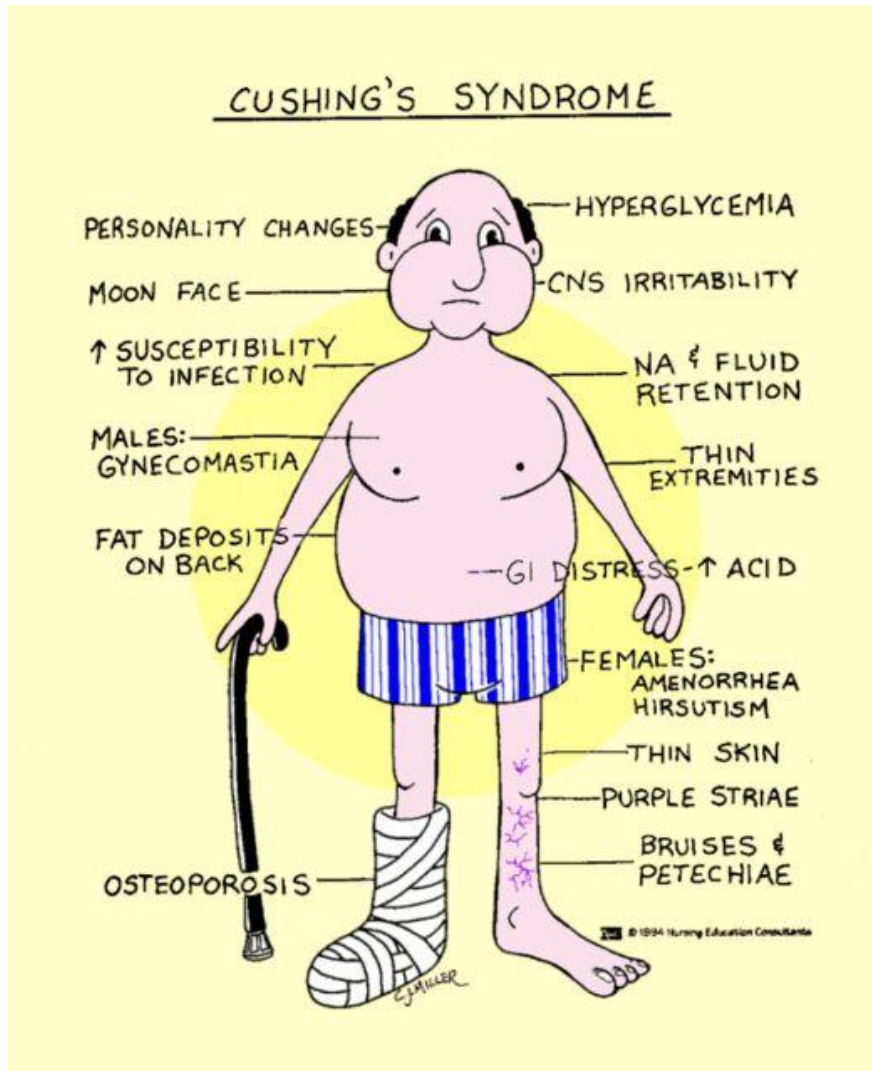
- The need for life long steroid replacement
- How to adjust medication in periods of illness
- How to recognise the signs of an adrenal crisis and how to give IM hydrocortisone in an emergency
- The need to make health professionals aware of the disease before care procedures e.g. doctors and dentists
- Advise they are entitled to free prescriptions
- Carry extra medication and a doctors letter when travelling
- Signpost to further advice and information at the Addisons Disease Self Help Group (www.addisons.org.uk)

Cushing's Syndrome

- Cushing's syndrome develops with an excess of cortisol hormone released by the adrenal glands. Symptoms usually develop gradually and so the diagnosis may not be clear for some time.
- If the source of the problem is the pituitary gland, then the correct name is Cushing's Disease. If it originates anywhere else, then the correct name is Cushing's Syndrome.



Cushing's: Symptoms



- Bruising, thin skin
- Central obesity, peripheral wasting and myopathy
- Hypertension
- Diabetes
- Low potassium
- Moon face and buffalo hump
- Gastric ulcers
- Psychological illness

Striae



Cushing's: Diagnosis

- Three diagnostic studies are currently recommended:
 - *late-night salivary cortisol*. Elevated cortisol between 11:00pm and midnight appears to be the earliest detectable abnormality. Cortisol secretion is usually very low at this time of the day, but is elevated in patients with Cushing's syndrome.
 - *24 hour urine free cortisol*. A 24 hour urine free cortisol level reflects the cortisol secretion throughout the day, so is elevated in patients with Cushing's.
 - *low-dose dexamethasone suppression*. Dexamethasone should suppress the cortisol production in normal subjects to a very low level. 1mg of dexamethasone is given at 11:00 p.m. followed by a measurement of serum cortisol early the following morning. Normal subjects should suppress their cortisol level to a very low level (<1.8 µg/dl).

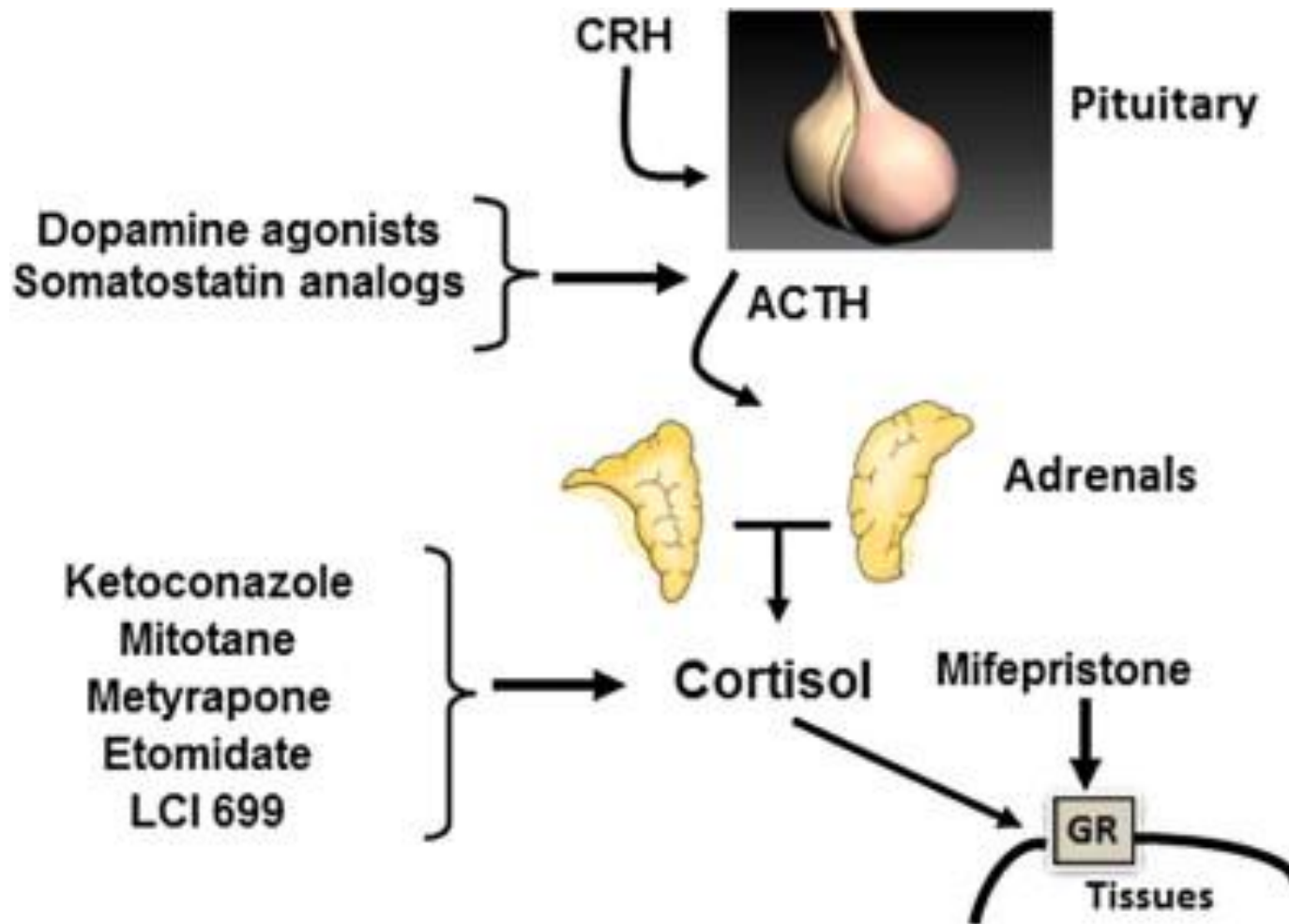
Cushing's: Treatment

- Treatments for Cushing syndrome are designed to lower the high level of cortisol and depends on the cause of the syndrome
- If the cause of is long-term use of corticosteroids then symptoms can be improved by reducing the dosage over a period of time
- If a pituitary tumour is the cause then surgery is needed. Removal of a tumour is curative in 80-85% of cases
- In patients where surgery is not possible or not curative there are a number of medications that can be used to reduce the level of cortisol produced by the adrenal glands

Medication for Cushings

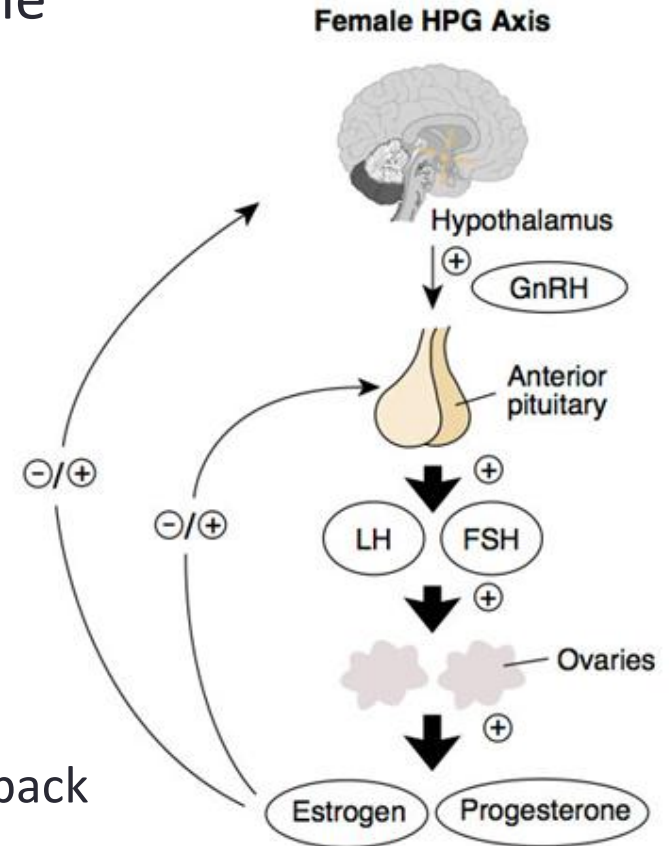
- There are medications that inhibit the adrenal gland production of cortisol. This group includes ketoconazole, mitotane, and metyrapone. All have side effects that limit usability and are successful in 50-80% of patients
- Pasireotide is the only licensed medication. It is given BD as a sc injection as it is a peptide. Pasireotide works by binding to somatostatin receptors.
 - Although it lowers cortisol in the majority of treated patients, pasireotide only *normalised* cortisol levels in about 25% of patients.
- The major side effect of pasireotide is increased blood sugars. 40% of patients experienced hyperglycaemia and nearly 1 in 5 develop diabetes.

Mechanisms of Action



Polycystic Ovary Syndrome (PCOS)

- The cause of polycystic ovary syndrome (PCOS) is unknown; it is likely to be multifactorial
- Complications include:
 - Impaired glucose tolerance and type 2 diabetes.
 - Infertility due to anovulation
- Common symptoms of PCOS include:
 - irregular periods or no periods at all
 - difficulty getting pregnant
 - hirsutism – usually on the face, chest or back
 - weight gain
 - thinning hair and hair loss from the head
 - oily skin or acne



PCOS: Diagnosis

- Polycystic ovary syndrome (PCOS) should be diagnosed if two of three of the following criteria are present, as long as other causes of menstrual disturbance and hyperandrogenism are excluded:
 - Infrequent or no ovulation (usually manifested as infrequent or no menstruation).
 - Clinical or biochemical signs of hyperandrogenism (such as hirsutism, acne, or male pattern alopecia), or elevated levels of total or free testosterone.
 - Polycystic ovaries on ultrasonography, defined as the presence of 12 or more follicles in at least one ovary, measuring 2–9 mm diameter, or increased ovarian volume (greater than 10 mL).

PCOS: Diagnostic Tests

- Total testosterone - this is normal to moderately elevated in women with PCOS.
 - If the testosterone level is significantly elevated other causes should be considered
- Sex hormone-binding globulin - this is normal to low in women with PCOS. It provides a surrogate measurement of the degree of hyperinsulinaemia.
- Measure the following to rule out other causes of oligomenorrhoea and amenorrhoea (such as premature ovarian failure, hypothyroidism, and hyperprolactinaemia):
 - Luteinizing hormone and follicle-stimulating hormone - may be increased in women with premature ovarian failure and decreased in women with hypogonadotropic hypogonadism.
 - Prolactin (normal range is less than 500 mU/L) - may be mildly elevated in women with PCOS.
 - Thyroid-stimulating hormone (normal range 0.4-4.5 mU/L)

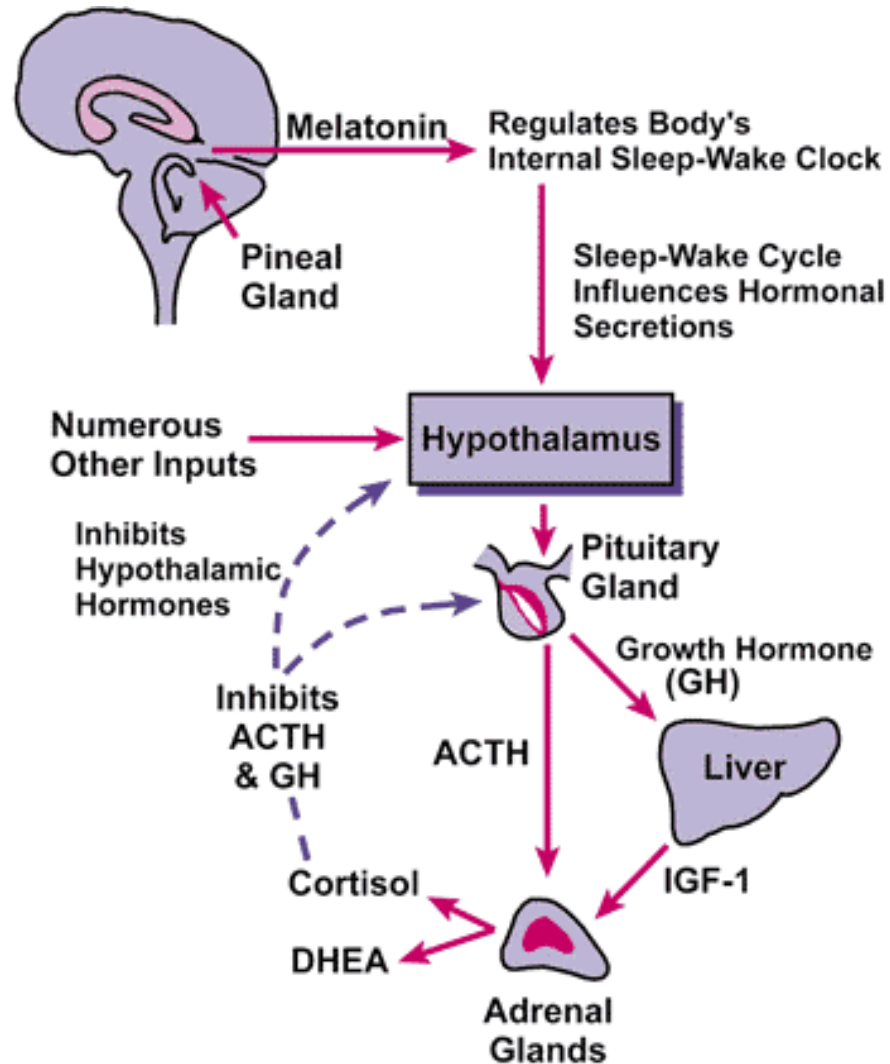
PCOS: Treatment and Advice

- **Polycystic ovary syndrome (PCOS) can't be cured, but the symptoms can be managed:**
 - Encourage a healthy lifestyle to reduce long-term risks (type 2 diabetes and cardiovascular disease)
 - Regular screening for impaired glucose tolerance and type 2 diabetes
 - Metformin isn't licensed for treating PCOS, but because many women with PCOS have insulin resistance, it is often used "off-label" to encourage fertility and control the symptoms.
 - Regular screening for cardiovascular risk factors and advise measures to reduce risk
 - For women who are overweight, advise weight loss
 - For women with infertility:
 - Carry out an assessment to identify the possible causes of infertility

Hirsutism Treatment

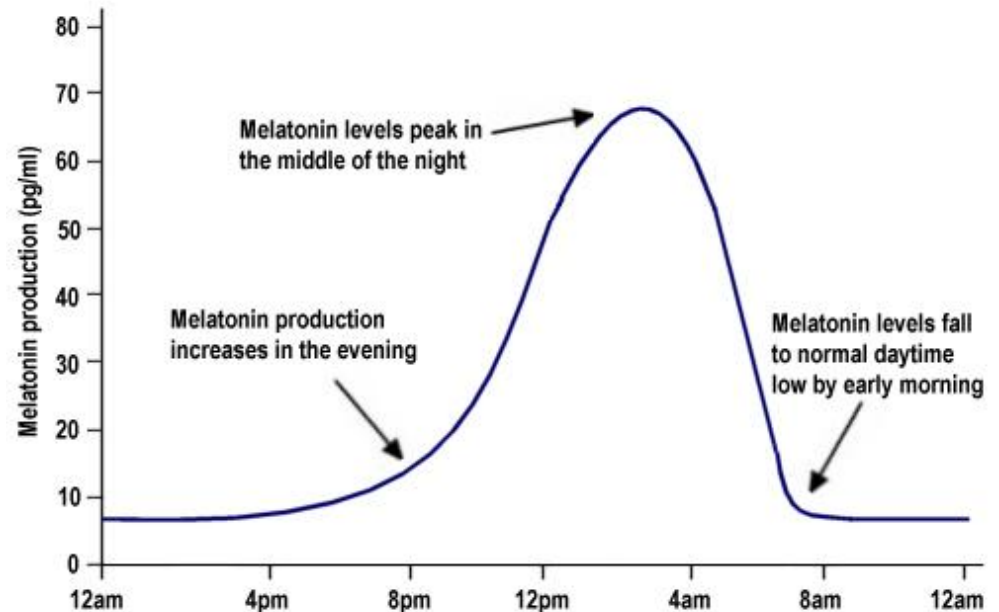
- One of the most troubling symptoms of PCOS is hirsutism (excessive hair growth) or alopecia (hair loss). There are a range of medications that can be used including:
 - particular types of combined oral contraceptive tablets (such as co-cyprindiol, Dianette, Marvelon and Yasmin)
 - cyproterone acetate
 - spironolactone
 - flutamide
 - finasteride
- These medications work by blocking the effects of androgens such as testosterone, and some also suppress production of these hormones by the ovaries.
- Eflornithine cream can also be used to slow down the growth of unwanted facial hair. This cream doesn't remove hair or cure unwanted facial hair.

Pineal Gland



Melatonin

- The production and release of melatonin from the pineal gland occurs with a clear daily (circadian) rhythm, with peak levels occurring at night.

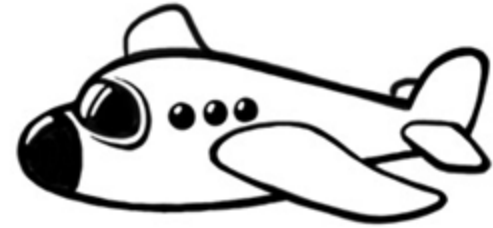


- The importance of pineal melatonin in human biology is not clear, although it may help to synchronise circadian rhythms in different parts of the body.
- Melatonin has often been called a 'sleep hormone' - although it is not essential for human sleep, we sleep better during the time that melatonin is secreted.
- In addition to its production in the body, melatonin can also be taken in capsule form. When administered at an appropriate time of day, it can reset the body's circadian rhythms.

Are melatonin supplements necessary?

- There are large variations in the amount of melatonin produced by individuals and these are not associated with any health problems
- The main consequences of large amounts of melatonin are drowsiness and reduced core body temperature. Very large doses have effects on the performance of the human reproductive system
- There is also evidence that very high concentrations of melatonin have an antioxidant effect, although the purpose of this has not yet been established
- Reduced melatonin production is not known to have any effect on health

Uses for melatonin



- Melatonin supplements are predominantly used to treat jet lag
- Some studies show that using it reduces how much jet lag people report on both eastward and westward flights, but other studies have not shown a benefit.
- Suggestions about times and dosages vary. Recommendations include:
 - Taking melatonin after dark the day you travel and after dark for a few days after arriving at your destination.
 - Taking melatonin in the evening a few days before you fly if flying eastward.
- Scientists are also looking at other uses such as:
 - Treating seasonal affective disorder (SAD)
 - Helping to control sleep patterns for people who work night shifts
 - Preventing or reducing problems with sleeping and confusion after surgery
 - Reducing chronic cluster headaches

References

NICE Clinical Knowledge Summaries (www.cks.nice.org.uk) :

- Hypothyroidism (April 2016)
- Hyperthyroidism (June 2016)
- Addison's Disease (March 2016)
- Polycystic Ovary Syndrome (Feb 2013)

NHS Choices (<http://www.nhs.uk/pages/home.aspx>)

Pituitary Foundation (<https://www.pituitary.org.uk/>)

Addison's Disease Self Help Foundation

(<http://www.addisons.org.uk/index.php/index.html>)

Cushing's Support and Research Foundation (www.csrf.net)

WebMD: Melatonin (<http://www.webmd.com/sleep-disorders/tc/melatonin-overview#1>)

