WHMC311

Session 26

Endocrine System Disease
Part I

Naturopathic Medicine
Department
Topic Overview

- Overview of principles and considerations in herbal management of the endocrine system.
- Review the anatomy and physiology of the endocrine system.
- Identify specific herbal medicines, drawing upon relevant literature, used in the support and modulation of hypothyroidism and hyperthyroidism.
- Discussion of relevant drug interactions and potenciations through an understanding of mechanisms of action of interactions.
Endocrine System Overview
Endocrine System

(Tortora & Grabowski, 2003)
Hormonal Triggering

(a) Circulating hormones

(b) Local hormones (paracrines and autocrines)

18.02

(Tortora & Grabowski, 2003)
Hormonal Activation & Protein Synthesis

1. Free hormone is released into the blood capillary.
2. The hormone binds to a transport protein and diffuses into the cell membrane.
3. The activated receptor-hormone complex alters gene expression in the cytosol.
4. Newly formed mRNA directs the synthesis of specific proteins on ribosomes.
5. New proteins alter the cell's activity.

(Tortora & Grabowski, 2003)
Cyclic AMP Response

1. Binding of hormone (first messenger) to its receptors activates G proteins, which activate adenylate cyclase.
2. Activated adenylate cyclase converts ATP to cAMP.
3. cAMP serves as a second messenger to activate protein kinases.
4. Activated protein kinases phosphorylate other enzymes.
5. Millions of phosphorylated enzymes catalyze reactions that produce physiological responses.
6. Phosphodiesterase inactivates cAMP.

(Tortora & Grabowski, 2003)
CRH, ACTH & Cortisol

(Tortora & Grabowski, 2003)
Pituitary Gland

(Tortora & Grabowski, 2003)
Hypothalamus

1. High blood osmotic pressure stimulates hypothalamic osmoreceptors

2. Osmoreceptors activate the neurosecretory cells that synthesize and release ADH

3. Nerve impulses liberate ADH from axon terminals in the posterior pituitary into the bloodstream

4. Kidneys retain more water, which decreases urine output

5. Low blood osmotic pressure inhibits hypothalamic osmoreceptors

6. Inhibition of osmoreceptors reduces or stops ADH secretion

ADH

Target tissues

Kidneys

Sudoriferous (sweat) glands decrease water loss by perspiration from the skin

Arterioles constrict, which increases blood pressure

(Tortora & Grabowski, 2003)
Naturopathic Diagnostics

- Dysfunctions of the Endocrine System may be seen at the Humoral Zone (Zone 3).
- Clinicians are further encouraged to consider the following regions when assessing the endocrine system: Thyroid & Para-Thyroid Glands, Heart, Pineal Gland, Pituitary Gland, Thymus Gland, Pancreas and Adrenal Glands.
Thyroid Gland

(Tortora & Grabowski, 2003)
Thyroid gland

1. Low blood levels of $T_3$ and $T_4$ or low metabolic rate stimulate release of TRH.
2. TRH, carried by hypophyseal portal veins to anterior pituitary stimulates release of TSH by thyrotrophs.
3. TSH released into blood stimulates thyroid follicular cells.
4. $T_3$ and $T_4$ released into blood by follicular cells.
5. Elevated $T_3$ inhibits release of TRH and TSH (negative feedback).
6. Actions of Thyroid Hormones:
   - Increase basal metabolic rate
   - Increase use of glucose and oxygen for ATP production
   - Stimulate synthesis of $Na^+/K^+$ ATPase
   - Increase body temperature (calorigenic effect)
   - Stimulate protein synthesis and accelerate tissue growth
   - Stimulate lipolysis and cholesterol excretion

(Tortora & Grabowski, 2003)
Thyroid Disorders

- Thyrotoxicosis
  - High levels of T3 and T4.
  - Symptoms: Palpitations, jitters, insomnia, irritability, weight loss, heat intolerance, fatigue, brittle hair, light flow in menses, warm/moist skin, hyperdefecation

- Hyperthyroidism
  - Graves’ (Parry’s or Basedow’s disease); thyroid multinodular goiter and toxic adenoma, Thyrotoxicosis (causes hyperthyroidism)

  (Friedman 2005, p.96)
Thyroid Disorders

Hypothyroidism

- Hashimoto’s (accounts for 90% hypothyroid cases); Drug induced (iatrogenic); Lithium (inhibits release of thyroid hormone); Amiodarone (contains high levels of iodine); Interferon alfa
  - Post-partum thyroid dysfunction
  - Sick Euthyroid Syndrome (SES)
    - Triggered by severe illness, physical trauma, physiological stress
  - Cretinism (from birth, due developmental abnormalities)
  - Subacute thyroiditis
  - Granulomatous, giant cell, or de Quervain’s thyroiditis
    (Gruner 2010 p328)
Stress and Thyroid Function

- Excess cortisol has an adverse effect on thyroid function.
- Elevated cortisol is seen in maladapation phase I and phase II.
- Elevated cortisol leads to:
  - ↓ active T3 and increases in reverse T3
  - ↓ peripheral hormone metabolism by inhibition of the enzyme 5’-deiodinase
  - ↑ risk of autoimmune disease, such as Hashimoto’s disease

(Hywood, 2004)
Hypothyroidism
Hypothyroidism

○ Primary causes
  • Iodine deficiency
  • Autoimmune disease: Hashimoto’s thyroiditis
  • Iatrogenic (radiation, surgery and drugs)

○ Main secondary cause
  • Hypopituitarism

  (Hywood 2004)

○ Tertiary hypothyroidism
  • Hypothalamus not releasing thyrotrophic-releasing hormone

  (Friedman 2005, p.98)
Hypothyroidism

- Other causes: Peripheral hypothyroidism, other pathologies, congenital disease, postpartum thyroiditis, organophosphate pesticides, toxic metal exposure, stress, nutrition, lifestyle (Friedman 2005, p.98)

- Can lead to disorders in the following systems (Haslett et al. 2002)
  - Cardio-respiratory
  - Neuromuscular
  - Haematological
  - Dermatological
  - Reproductive
  - Gastrointestinal
Hashimoto’s Disease

- An autoimmune disease, also known as chronic lymphocytic thyroiditis, where the thyroid gland is gradually destroyed by a variety of cell and antibody mediated immune processes. Diagnosed by:
  - Enlargement of the thyroid, known as a goitre
  - High levels of antibodies against thyroglobulin (TG) and thyroid peroxidase (TPO), detected via blood test
  - Fine needle aspiration of the thyroid (also known as a needle biopsy), which shows lymphocytes and macrophages
  - A radioactive uptake scan, which would show diffuse uptake in an enlarged thyroid gland
  - Ultrasound, which would show an enlarged thyroid gland

(Wiebolt et al 2011)
Clinical Features

- Since thyroid function affects the metabolism of virtually every organ system in the body, the signs and symptoms of hypothyroidism are diverse. S + S are generally subtle presentations of the disease and therefore hypothyroidism is often left undiagnosed for years.

- General feature
  - Tiredness, fatigue, weight gain, cold intolerance, hoarseness, goitre, drug hypersensitivity (narcotics, barbiturates, anaesthetics)
  - Neuromuscular
  - Muscular stiffness, aches and pains, carpal tunnel syndrome, ataxia

(Erdogan 2009)
Clinical Features

- CNS (Depression, memory and mental impairment, irritability, slurred speech)
- Dermatological (Dry flaky skin, alopecia, coarse dry hair, pale or yellowed skin)
- Reproductive (Irregular or heavy menses, infertility, decreased libido)
- Gastrointestinal (Constipation, flatulence)
- Cardiovascular (Bradycardia, angina, cardiac failure, hypertension, hyperlipidaemia)
- Other (Anaemia, deafness) (Erdogan 2009)
Pharmaceutical Management

Thyroxine (T4) & Liothyronine (T3)

Mode of Action

- Both forms are absorbed in the GIT. T4 is metabolized to T3 in peripheral tissue. T3 is ten times more biologically active than T4 as it does not require conversion.

Side Effects

- Usually present with excess pharmacodynamics, presentation is hyperthyroid (palpitations, nervousness, insomnia, tremor, reduced bone density).
- These symptoms resolve with appropriate dosage.
- T3 has potential to be a cardio toxic agent

(Bullock et al, 2007)
Herbal Actions

- Iodine-containing herbs
- Thyroid supporting herbs
- Bitters
- Nervines
- Immune modulators – prescription of herbs exhibiting an immune suppressant action
- Anti-inflammatories
- Hepatics and hepato-protectives

(Yarnell & Abascal 2006)
Fucus vesiculosus

- Common name: Bladderwrack

- Actions
  - Anti-obesity
  - Demulcent
  - Thyroid modulator
  - Anti-rheumatic (Bone 2003 p103)
Fucus vesiculosus

- Medicinal Uses
  - The iodine content of Fucus in conjunction with other minerals is believed to stimulate the thyroid gland
  - It may enhance the ability of some patients with thyroid deficiency which is not due to a simple lack of iodine, to make use of iodine
  - It is a more potent stimulator of thyroid function than inorganic iodine
  - May increase basal metabolic rate and by assisting lipid metabolism
  - Weight loss in obesity  (Bone 2003 p104)
Withania somnifera

- Panda and Kar (1998 cited in Bone 2004:24) found that an extract of *Withania somnifera* root (given to male mice at an oral dose of 1.4 g/kg for 20 days) significantly increased serum $T_3$ and $T_4$ concentrations.

- The largest change was for $T_4$, which was increased by 111% compared to controls. The change in $T_3$ was a modest 18%.

- The results of this study were confirmed by the same researchers in another model, this time using female mice (Panda and Kar 1999:233).
Bacopa monnieri

- Kar, Panda and Bharti (2002:281) continuing investigating the effects of herbs on thyroid hormones, and found that an extract of Bacopa monnieri leaf (given to male mice at an oral dose of 200 mg/day for 15 days) also significantly boosted T4 by 41%, suggesting a thyroid-stimulating role.

- Bacopa had no impact on levels of T3.

- Its brain tonic effects are also highly desirable in hypothyroidism (Hywood 2004)
Coleus forskohlii

- Forskolin catalyses the production of cAMP
- TSH requires cAMP as a secondary messenger → this potentiates the intracellular effects of many hormones, including TSH
- Forskolin is a potent activator of adenylate cyclase in many tissues including the thyroid gland (van Sande, Cochaux & Dumont 1982:137; Fradkin et al. 1982:849)
- Laurberg (1984:273) compared the effects of 10(-5) M forskolin and 100 mu units/ml TSH on the dynamics of T4 and T3 secretion from perfused dog thyroid lobes (Bone 2004, p.24)
Commiphora mukul

- Guggul (*Commiphora mukul*), has developed a reputation as a thyroid stimulating herb, has been found to have no effect on T4 levels.

- Guggul did however, boost T3, which implies that it enhances peripheral conversion of T4, rather than having any direct effect on thyroid output. (Bone 2004, p.24)
Adjunct Treatments

- If thyroid antibodies are high, (an indication of active thyroid destruction), the protocol for autoimmune diseases would also be included. eg.
  - Immune modulators, eg: *Echinacea spp.*
  - Antivirals eg: *Hypericum perforatum*
  - Antioxidants eg: Grape seed / *Curcuma longa*
  - Antiinflammatory herbs eg: *Rehmannia glutinosa, Bupleurum falcatum, Hemidesmus indicus*

- Also worth considering is the potential for gut dysbiosis involvement
  (Hywood 2004)
Drug-Herb Interactions

Thyroxine & Liothyronine

Thiocyanates & Goitrogens

- Inhibits the body’s absorption or utilisation of iodine, increasing the requirement for synthetic T4 & T3
  (Dal Maso et al. 2009)

*Fucus vesiculosus* (Bladderwrack)

- Concurrent utilisation may increase the requirement for synthetic T4 & T3 (Habra & Sarlis, 2005)
Drug-Herb Interactions

Thyroxine & Liothyronine

*Withania somnifera*

- Withania has been shown to enhance serum T3 & T4 concentration in mice (Mishra et.al. 2000 p342)

*Eleutherococcus senticosus* (Siberian ginseng)

- Siberian ginseng will be of benefit in hypothyroid patients to counter symptoms such as fatigue, depression, reduced mental function.
Drug-Herb Interactions

Thyroxine & Liothyronine

*Coleus forskohlii* (Coleus)

- Theoretical concern as forskolin activates increased cyclic AMP in vitro so may potentiate effects of prescribed drug (monitor, low level risk)
- Study demonstrated that forskolin stimulated thyroid function with increased thyroid hormone production in isolated organ.
- However, low concentrations of forskolin inhibited thyroid function in vitro (thyroid cells)
- Clinical significance unknown (Bone 2003, p.156-157)
Drug-Herb Interactions

Thyroxine & Liothyronine

*Apium graveolens* (Celery)
- Reduced drug effect; low clinical significance

*Armoracia rusticana* (Horseradish)
- Increased drug requirement; thought to be goitrogenic – inhibits thyroxine formation (*Deme et al* 1985)
Drug-Herb Interactions

Thyroxine & Liothyronine

*Lycopus virginicus*
- Contraindicated, may interfere with action of thyroid hormone (Bone 2005, p.298)

*Trigonella foenum-graecum*
- High doses (animal trials) significantly decreased serum T3 concentration and T3/T4 ratio, but increased T4 levels in mice (Bone 2005, p.401)

*Leonurus cardiaca*
- Antithyroid activity, used for mild thyroid hyperfunction (Bone 2005, p.510)
Hyperthyroidism
Hyperthyroidism

- The clinical syndrome which results from exposure of the body tissues to excess circulating levels of thyroid hormones (T3, T4) which are stimulated by thyroid activity (Gruner 2010 p325)

- Hypersecretion increases oxygen use by cells, elevates heat production & increased appetite – can lead to thyrotoxicosis (‘thyroid storm’)

- A ‘thyroid storm’ is an aggravation of all symptoms in hyperthyroidism with fever & rapid heart rate – potentiated by trauma, surgery, emotional stress, labour during child birth. (Mistovich et al 2007)
Hyperthyroidism

Clinical Features and Complications:
- Heat intolerance, Increased sweating
- Weight loss with increased appetite
- Diarrhoea
- Palpitations, Tachycardia
- Raised systolic blood pressure
- Shortness of breath on exertion
- Nervousness and irritability
- Muscular weakness (thyrotoxic myopathy)
- Shaking of the hands
- Loss of hair
- Pruritus
- Swelling of eye lids (Hershman 2008)
Graves’ Disease

- Body produces antibodies that mimic TSH activity which are not regulated by normal negative feedback mechanisms therefore thyroid gland constantly stimulated to grow & produce thyroid hormones

- Goitre - enlarged thyroid, 2 – 3 times normal size

- Exophthalmos (protruding eyes – oedema behind eyes)
Signs and Symptoms

Symptoms of hyperthyroidism include:

- Increased metabolic rate, frequent bowel movements
- Heat intolerance
- Excessive sweating
- Weight loss despite increased food intake
- Insomnia
- Tremor of extended fingers
- Nervousness (Gruner 2010,p338)
Thyroid Levels

- Blood tests reveal elevated T4 & T3 levels

- TSH is subnormal in the hyperthyroid stage, normal in the euthyroid stage, and above normal if the patient becomes hypothyroid

- Presence of autoantibodies - including "long acting thyroid stimulators" (LATS). [Now more commonly known as TSH receptor antibodies] (Gruner 2010,p328)
Pharmaceutical Management

Anti-thyroid Drugs - Carbimazole

Mode of Action
- Blocks the organic binding of iodine through inhibition of iodination of tyrosine. Has some affect on peroxidase - required catalyst in thyroxine synthesis.

Side Effects
- Nausea, GI distress, headache, rashes, bone marrow depression, hematological disturbances, myopathy, arthralgia, pruritus, urticaria, alopecia, hepatic effects.

(Bryant & Knights, 2011)
Pharmaceutical Management

**Anti-thyroid Drugs** - Propylthiouracil

**Mode of Action**
- Blocks peripheral conversion of thyroxine ($T_4$) to triiodothyronine ($T_3$) by inhibiting the enzyme 5-deiodinase.

**Side Effects**
- Haematopoietic effects, hypothyroidism, thyrotoxicosis, itching.

(Bryant & Knights, 2011)
Pharmaceutical Management

Radioactive Iodine

Mode of Action
- Oral administration of radioactive iodine that is taken up by the thyroid that irreversibly damages thyroid nodule function.

Side Effects
- Transient damage to mouth, throat & GIT
- Nausea, vomiting
- Irritability, fatigue
- Symptoms pass within 2-4 weeks

(Bryant & Knights, 2011)
Herbal Treatment

- Dampen thyroid function with TSH antagonists
  - Bugleweed
  - Address cardiac symptoms (tachycardia, palpitations) with antiarrhythmic i.e. Motherwort (Gruner 2010, p.335)

- Balance immune system function
  - With immune modulator e.g. Echinacea (Bone 2003, p.491)
  - And immune suppressant e.g. Hemidesmus (Bone 2003, p.491)

- Reduce inflammation with anti-inflammatories
  - Rehmannia, Bupleurum (Bone 2003, p.489)

- Antivirals
  - Hypericum, Thuja (Bone 2003, p.490)
Herbal Treatment

Actions required
- Thyroid modulators
- Immune modulators
- Relaxing nervines
- Bitters
- Cardiac tonics

(Gruner 2010, pp335-8)
Lycopus europaeus

- Common name: Bugleweed

- Actions
  - Cardio-active diuretic
  - Peripheral vasoconstrictor
  - Anti-haemorrhagic
  - Thyroxine antagonist
  - Sedative

  (Bone 2003, p.113)
**Lycopus europaeus**

- Lycopus extracts are used in folk medicine for the treatment of hyperthyroid symptoms.

- Diverse effects on the pituitary thyroidal system as well as on the pituitary gonadal system have been confirmed in experimental studies.

- Winterhoff et al (1994, p.41) investigated a ethanolic extract of *Lycopus europaeus* when applied orally to rats.
Lycopus europaeus

- Endocrine System
  - Grave's disease
  - Hyperthyroidism
  - Thyrotoxicosis - dyspnoea, tachycardia & tremor
- Cardiovascular System
  - Nervous tachycardia
- Respiratory Tract
  - Haemoptysis
  - Irritating coughs with copious sputum
- Contraindications: Hypothyroidism
**Melissa officinalis**

- **Common name:** Lemon Balm

- **Actions**
  - Carminative
  - Anti-spasmodic
  - Relaxant
  - Diaphoretic
  - TSH antagonist (Bone 2003, p.308)

- Santini et al (2003, p.950) found *Melissa officinalis* to produce a significant inhibition of TSH binding to its receptor and a significant inhibition of antibody binding to TSH.
Melissa officinalis

- Endocrine System
  - Demonstrated an antagonistic effect on thyroid stimulating hormone (TSH) by interfering with its ability to bind target cells and also by its inhibition of the enzyme responsible for producing T3
  - It inhibits the immunological binding that stimulates thyroid output in Grave's disease.
  - Grave's disease
  - Hyperthyroidism

(Bone 2003, p.308)
Leonurus cardiaca
Leonurus cardiaca

- Common name: Motherwort

- Potential indications
  - Adjuvant therapy for hyperthyroidism through the relief of palpitations and tachycardia (Weiss 1988, p.279).
  - Nervous cardiac disorders such as palpitations
  - Coronary heart disease
  - Anxiety, neuralgia, chorea
  - Amenorrhoea, dysmenorrhoea, ovarian pain

- Motherwort is considered in European herbal medicine as having anti-thyroid activity (Bone 2003, p.331).
Hemidemus indicus

- A traditional Ayurvedic herb used in the treatment of immunological disorders

- Therapeutic actions
  - Depurative
  - Demulcent
  - Diaphoretic
  - Immuno-suppressant
Hemidemus indicus

- Hemidesmus has been found to depress both the cell mediated and humoral components of the immune system. (Bone 2003, p.275)
- Specific indication - autoimmune disease
- Combines well with Picrorrhiza kurroa
- Although it has immune depressing properties it is a safe and non-toxic herb

(Bone 2003, p.275)
Bupleurum falcatum
Bupleurum falcatum

- **Actions**
  - The main Chinese herb used for liver disharmony
  - Anti-inflammatory
  - Adaptogen
  - Hepatoprotective
  - Mild sedative
  - Potent anti-tussive

- **Precautions:**
  - Bupleurum has a slight sedative effect in some patients
  - It may also increase bowel movements and flatulence
Bupleurum falcatum

Medicinal Uses
- Enhances the anti-inflammatory action of glucocorticoids
- Saikosaponins stimulate ACTH secretion from the pituitary and thereby stimulate endogenous production of cortisol
- This is accompanied by a marked but transient increase in blood glucose
- In animal experiments it was found that the weight of the adrenal glands increased in proportion to the dosage of saikosaponins
Sub Acute Thyroiditis

Granulomatous, giant cell, or de Quervain’s thyroiditis

- Viral origin
- Symptoms usually follow URIs, include pronounced asthenia, malaise, pain over thyroid or referred to lower jaw, ear, or occiput.
- Less common, acute onset with severe pain over thyroid, fever, sometime thyrotoxicosis.
- Symptoms may continue (smolder) for weeks/months & eventually subside with return to normal thyroid function.
Drug-Herb Interactions

General Interactions

Iodine

- Kelp, iodine containing supplements and drugs (iodinated contrast agents, amiodarone) can increase T4 synthesis. Responses are greater in those individuals that present with sub-acute hyperthyroidism or an underlying goitre.

  (Habra & Sarlis, 2005; Kumar & Clark, 2009)

Guggul (monitor, low level risk)

- May reduce effectiveness of hyperthyroid medication (carbimazole). Theoretical based on in vivo animal study.

  (Braun & Cohen, 2010)
Goiter
Goiter

- Diffusely enlarged thyroid gland; usually 2-3 times the normal volume, and increased blood flow may manifest thrill or bruit

- In some patients, particularly the elderly, no thyroid enlargement is palpable or the gland may be nodular

- The largest goiters tend to occur in young men.

(Davidson & Haslett, 2002)
Goiter

- Ophthalmopathy
  - Increased exposure of the cornea, resulting from proptosis and lid retraction
  - More common in cigarette smokers

- Orthodox treatment
  - Carbimazole
  - Propylthiouracil

- These drugs reduce the synthesis of new thyroid hormones by inhibiting the iodination of tyrosine.

(Davidson & Haslett, 2002)
Pre-reading for next session

- **Reading 1:** Beera, A Wiebelitza, K Schmidt-Gayk, H 2008, “Lycopus europaeus (Gypsywort): Effects on the thyroidal parameters and symptoms associated with thyroid function” *Phytomedicine* Volume 15, pp.16–22 (Via science direct)

References

- Bone K., 2004, Bacopa and Withania: effects on Thyroid Function, Modern Phytotherapist, Vol.8, No.2. pp24-25
References

• Friedman M 2005, Fundamentals of Naturopathic Endocrinology, CCNM Press, Toronto, Canada
• Higgins C, 2007, Understanding Laboratory Investigations for Nurses and Health Professionals, Blackwell, Oxford
• Hywood A., 2004, Effective Herbal Approaches to Thyroid Dysfunction, MediHerb InClinic seminar series notes
References

References

• Weiss RF, 1988, Herbal Medicine, Bath pres, Avon.