Veterinary Bioscience: Cells to Systems

Lecture 14– Hormones and their regulation

Lecturer: Prof. Simon Bailey **Email:** bais@unimelb.edu.au

Intended Learning Outcomes

1. For each of the different groups of hormones, be able to describe their site of production and main biological function - in order to understand disease processes where glandular tissues are affected or hormone actions are increased or decreased.
2. Describe (using specific hormone examples) how hormone secretion is regulated and how negative and positive feedback processes modify their secretion; in order to understand how certain pathological processes can interfere with the production of a hormone.

Keywords
Hormones, endocrinology, insulin, steroids, catecholamines, thyroid hormones, eicosanoids

MAIN CHEMICAL AND PHYSIOLOGICAL CLASSES OF HORMONES

Hormones fall into four general chemical classes:
1) Peptides and proteins
2) Steroids
3) Amines (Tyrosine derivatives). Catecholamines and thyroid hormones
4) Eicosanoids:—prostaglandins, prostacyclins, leukotrienes and the thromboxanes

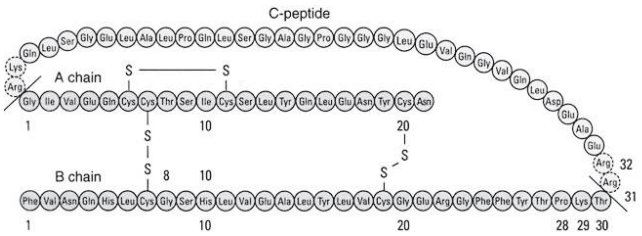
Chemical Nature of the classical hormones – examples:

Tyrosine derivatives	**Steroids**	**Peptides (<20 amino acids)**	**Proteins (>20 amino acids)**
Adrenaline	Testosterone	Oxytocin	Insulin
Noradrenaline	Estradiol	Anti diuretic hormone	Glucagon
Dopamine	Progesterone	Angiotensin II	Prolactin
Triiodothyronine	Cortisol	Thyrotropin releasing	Growth hormone
Thyroxine	Aldosterone	hormone	Adrenocorticotropic hormone
			Thyroid-stimulating hormone

1) Protein or peptide hormones:

The majority of all hormones are either peptides (<20 amino acids) or proteins(>20 amino acids) e.g. hypothalamic releasing and inhibiting hormones, anterior and posterior pituitary hormones, insulin, glucagon and parathyroid hormone are all examples of peptide and protein hormones.

Peptide and protein hormones are initially synthesized as prohormones, which are cleaved by proteolytic enzymes to form hormones that are packaged within Golgi apparatus into secretory vesicles. Following stimulation of the cell the contents of the secretory vesicles are released via exocytosis usually via a change in calcium levels.



The protein structure of proinsulin. C-peptide is cleaved away by hydrolysis, to produce insulin which consists of two chains of 21 and 30 amino acids (A chain and B chain), connected by two disulfide bridges.

Protein and peptide hormones are relatively polar molecules and as such are soluble in aqueous solvents (water soluble). They are thus hydrophilic (lipophobic) and as such are transported as free hormone in the blood. They circulate as free unbound proteins, and have a short half life of only a few minutes in the blood. Hydrophilic hormones are unable to diffuse across the plasma membrane and must bind to cell surface receptors to mediate an effect. The binding of the peptide hormone to the cell surface receptor results in activation of a second messenger system which results in a cascade effect altering the activity of pre-exisiting proteins and enzymes that mediate an effect.

An example of a protein hormone -Insulin

a. Insulin is produced by beta cells of the pancreas and its main functions are to decrease blood glucose and promote anabolic storage. It is secreted in times of excess nutrient availability which allows carbohydrates to be used as an as energy sources and store excess nutrients as glycogen or triglycerides.
b. Main targets: Liver, adipose tissue and muscle
   - In liver, insulin facilitates storage of glucose as glycogen and triglycerides
   - In muscle insulin promotes the uptake of glucose via activation of Glut -4 transport channels and promotes glucose conversion into glycogen
   - In adipocytes, insulin promotes uptake of glucose which is converted into triglycerides for storage

In healthy animals, plasma [glucose] fasting levels are usually 4 and 5 mM. Following food intake the plasma [glucose] rises but does not normally exceed 10 mM. Even small increases inplasma [glucose] can initiate insulin secretion from the the β cells in the pancreas. Here increased glucose enters the β cells in the pancreas and is the best secretagogue for insulin release but some amino acids (especially arginine,leucine and leucine), and other sugars eg galactose and mannose can also weakly stimulate insulin secretion. ATP generated from the metabolism of these varied substances is thought to lead to depolarizing the islet cell membrane by reducing intracellular [K+] by opening up an ion channel which inturn releases calcium and induces insulin secretion. There are a number of hormones such as glucagon, growth hormone, adrenalin and cortisol that can balance blood glucose levels by releasing glucose but insulin is the only hormone that lowers blood glucose.

2) Amine hormones

All amine hormones are nitrogen containing derivatives of the amino acid tyrosine. They include:

a) the thyroid hormones (eg. thyroxine & triiodothyronine which are iodinated forms of tyrosine derivatives) and
b) the hormones produced by the adrenal medulla (catecholamines; eg adrenaline and noradrenaline).

Catecholamines

The catecholamines differ from the thyroid hormones in that they are:-

- Hydrophilic and are transported in blood 50% bound to proteins.
- Stored in chromaffin granules
- Released following exocytosis of granules
- Bind to alpha and beta adrenergic receptors on cell surface
- Activate a second messenger system often via G proteins

Stress is the major stimulation of adrenalin or epinephrine release eg threat, noise, excitement, high temperature

The catecholamines are synthesised in sequence from tyrosine via L-Dopa, Dopamine Noradrenalin and adrenalin.
Sympathetic stimulation important in activating key enzymes in biosynthetic pathway such as tyrosine hydroxylase and dopamine □-hydroxylase
Catecholamines have a short half life. No negative feedback loop.
Action is stopped mainly by degradation

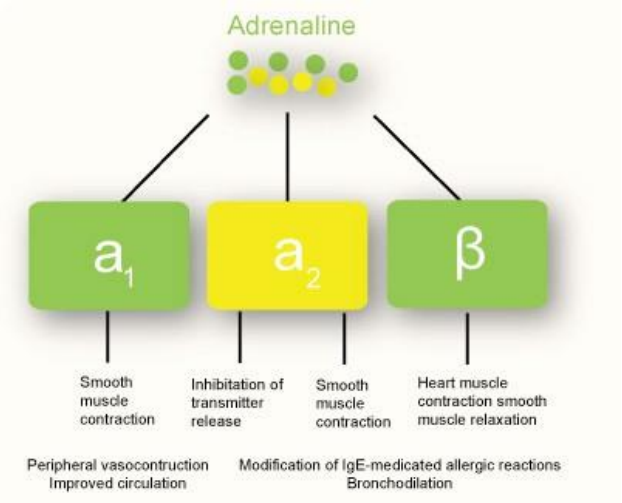
E.g. Adrenalin: Causes an increase in heart rate, increased blood pressure and relaxation of smooth muscles in the lungs.

The response varies in different tissues depending upon the type of adrenergic receptor activated. Activation of alpha-adrenergic receptors induces vasoconstriction and glycogenolysis (increasing blood glucose levels) whereas stimulation beta-adrenergic receptors cause vasodilation, increased heart contraction, lipolysis and bronchodilation

The catecholamines differ from the thyroid hormones in that they are: -

- Hydrophilic and are transported in blood 50% bound to proteins.
- Stored in chromaffin granules. --à Released following exocytosis of granules
- Bind to alpha and beta receptors on target cell surfaces.
- Activate a second messenger system.

Adrenalin through its action on alpha-adrenergic receptors, adrenaline causes smooth muscle contraction. Through its action on beta-adrenergic receptors increase cardiac output by increasing heart rate and force of contraction to increase blood pressure. Its metabolic actions include increasing hepatic glucose output and lipogenesis.



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Thyroid Hormones

Thyroid hormones are made from tyrosine and iodine

Lipid soluble (lipophilic) are largely transported bound to plasma proteins. Stored in colloid

Have cell membrane transporters to facilitate entry into cells Bind to receptors inside cells

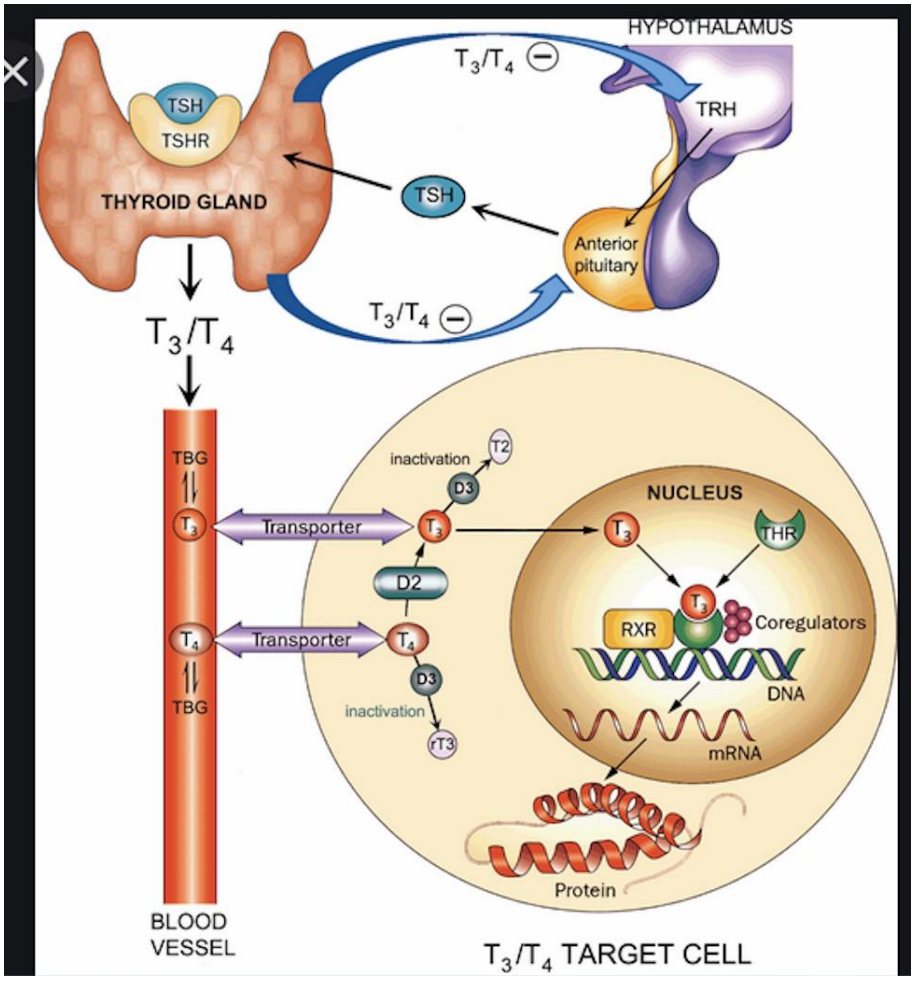
Activate specific genes to produce new proteins
Thyroid hormones have major effects on:

1. Metabolic rate
2. Oxygen utilization
3. Nutrients mobilization and utilization
4. Thermogenesis

Hormones produced	Target	Function
Thyroid follicular cells Tetraiodothyronine (T4) & Triiodothyronine (T3)	Most cells	Regulate metabolic rate and are essential for nerve development brain function & normal growth.

Negative Feedback

Stimulus for release of thyroid hormone is via thyroid releasing hormone from the hypothalamus which releases thyroid stimulating hormone from the anterior pituitary. The pathway undergoes negative feedback at level of thyrotropes in anterior pituitary reducing TSH secretion or at level of hypothalamus reducing TRH secretion.



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3) Eicosanoids

- Eicosanoids are a family of signalling molecules that act as paracrine hormones and include prostaglandins (PGE, PGF), prostacyclin (PGI2), leukotrienes (LTs) and thromboxanes (TXA).
- Derived from membrane phospholipids and form arachidonic acid in presence of phospholipase A2

- Two pathways
    - Cyclooxygenase (COX)
    - 5-lipoxygenase (5-LO)

1. **COX pathway**
    - Two different forms of COX enzyme COX1 which is constitutive and COX2 that is inducible during inflammation
    - Arachidonic acid is converted to cyclo-endoperoxides in presence COX enzyme
    - Enzymes, many of which are tissue specific, then convert the cyclo- endoperoxides into the final biologically active thromboxane, prostaglandin or prostacyclin molecule.

- **Thromboxanes (TXA)**

  Produced by platelets acts via Gq pathway and causes arterial vasoconstriction and platelet aggregation

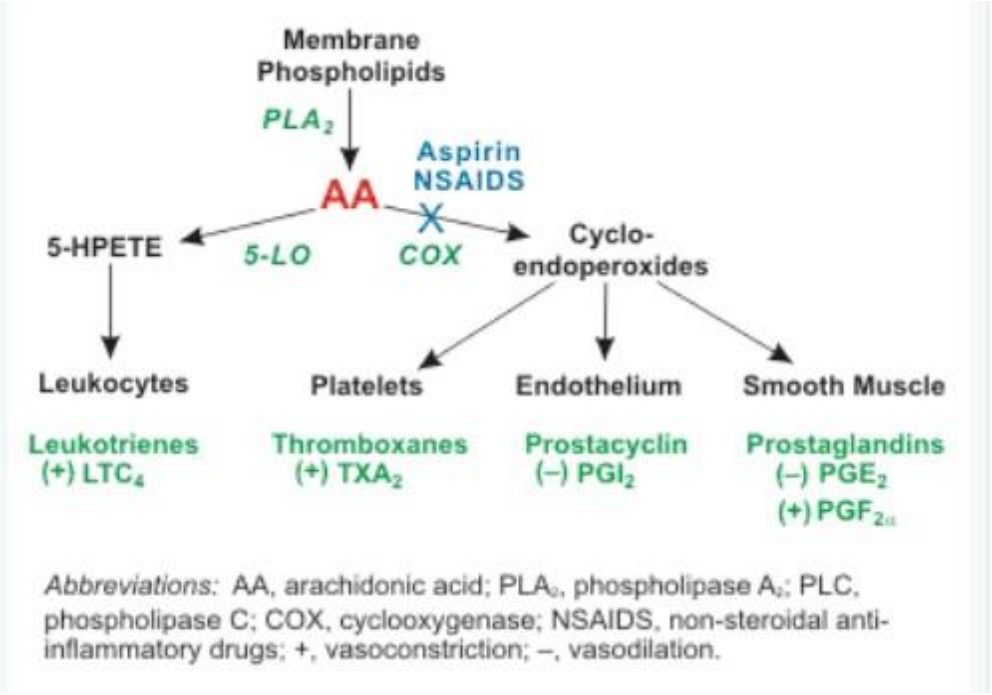
- **Prostaglandins**

  PGE2 produced by smooth muscle cells acts via a Gs pathway is a vasodilator and regulate blood flow whereas PGF2 is acts via a Gq pathway and is a vasoconstrictor **Prostacyclin**
  - Potent vasodilator and inhibitor of platelet adhesion to endothelium produced by vascular endothelial cells via Gs stimulatory pathway

2. **Lipoxygenase pathway**

- Leukotrienes eg LTC4 promote vascular permeability and leukocyte chemo -attractant are produced by leucocytes following inflammation and tissue injury

- **Drug effects**
  - Corticosteroids block the entire pathway at the level of PLA2 hence inhibiting leukotrienes TXA, prostacyclin and prostaglandins
  - Non steroidal anti inflammatory drugs block pathway at COX enzyme level so leukotriene pathway via 5-Lo still active while prostaglandins PGI and TXA inhibited



https://www.cvphysiology.com/Blood%20Flow/BF013

Examples of some actions of selected eicosanoids

PGE_2	Smooth muscle contraction fever bronchoconstriction	PGI_2	Inhibition of platelet aggregation vasodilation
$PGF_{2\alpha}$	Uterine contraction	LTB_4	Leukocyte recruitment
TXA_2	Platelet aggregation vasoconstriction	LTC_4, LTD_4	Anaphylaxis; bronchial smooth muscle contraction.

4) Steroid Hormones

Classification of steroid hormones is into 5 families primarily based upon receptor binding . Glucocoticoids (cortisol) , mineral corticoids (aldosterone), androgens (testosterone) , estrogens (estradiol) and progestogens (progesterone).

1) Adrenal cortex secretes cortisol, corticosterone & aldosterone
2) Ovaries secrete estrogen and progesterone
3) Testes secrete testosterone
4) Placenta secretes estrogen and progesterone.

Steroid hormones are derived from **cholesterol**. Although steroid producing endocrine glands synthesize some of their own cholesterol from acetate , their major source is the cholesterol delivered to the cells by low density lipoproteins that are made in the liver and circulate in blood. Cholesterol is stored (or its derivatives) in lipid droplets within each steroidogenic organ and cholesterol is transported from the cytoplasm to mitochondria.

Biosynthesis of steroid hormones requires a series of oxidative enzymatic reactions that modify cholesterol molecules in mitochondria or the endoplasmic reticulum by modifying side chains attached to them. Each steroid-producing organ only produces those steroid hormones for which it has a complete set of enzymes. Steroid hormones are not stored (though cholesterol precursors are stored in lipid droplets), and once formed, these lipid soluble hormones exit the cell into the blood by diffusion. Because they are not stored, increases in secretion reflect accelerated rates of synthesis. The first step in the synthesis of steroid hormones is the conversion of cholesterol to pregnenolone by enzyme CYP11A1 (cholesterol desmolase)

Steroid hormones are largely non-polar and lipophilic and are transported in the blood bound to plasma proteins such as albumin (nonspecific) or specific binding proteins eg transcortin. Binding to proteins extends their half-life by acting as a reservoir and also inhibits their rate breakdown and elimination. At target sites steroid hormones diffuse across the plasma membrane and are able to bind to specific receptors inside cells either within the cytosol or nucleus. The resulting hormone-receptor complexes bind to hormone response elements (HRE) on DNA (transcription- control regions) in DNA thereby affecting expression of specific genes to produce new proteins.

Cortisol

Cortisol synthesized in the zona fasciculata layer of the adrenal cortex through a series of enzymatic reactions

- Cholesterol to pregnenolone (rate limiting step).

Metabolic Actions of cortisol:

- Maintains glucose homeostasis
- Defence against hypoglycaemia.
- Increase plasma glucose
- Liver Increased glucose output
- Promotes gluconeogenesis, glycogenolysis & lipolysis
- Prior action of cortisol
- Build up of glycogen stores
- Reduce inflammatory responses by inhibiting eicosanoid formation

Regulation of cortisol secretion is via a feedback loop involving ACTH produces by corticotropes in the anterior pituitary and corticotrophin releasing hormone via hypothalamus but cortisol can be stimulated to be released via physical, chemical and emotional stimuli induced by stress and other factors.

Positive feedback

Oxytocin (OT)

OT is a neuropeptide that stimulates smooth muscle contraction by the uterus during parturition and by the mammary gland during suckling. Receptors for OT are Gill q-protein coupled and are located on uterine smooth muscle (myometrium & endometrium) and myoepithelial cells of the mammary gland. In lactating animals OT acts on the myoepithelial cells which surround the alveoli and ducts of the mammary gland to contract and to release milk (milk let-down) into a collecting chamber from where it can be extracted by sucking at the nipple.

The sucking process stimulates nerve endings in the nipple and via afferent neural pathway in the spinal cord triggers rapid bursts of OT from the posterior pituitary. This is an example of positive regulation (feedback). Other different psychic stimuli (eg crying) may also promote OT release and it may act as a neurotransmitter in brain regulating maternal behaviour and sexual arousal. OT also affects uterine contractions during partition. Stretching of the uterus at onset of parturition apply mild stretch to cervix. In response to sensory input from the cervix OT is secreted from hypothalamus and stimulates further contractions of uterine smooth muscle.

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