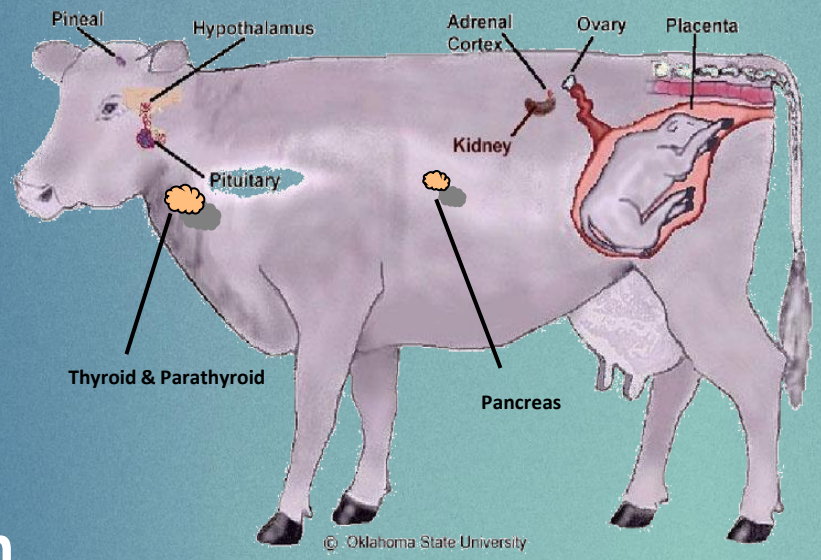
THE UNIVERSITY OF MELBOURNE
Faculty of Veterinary and Agricultural Sciences



Lecture 14
Hormones and their regulation

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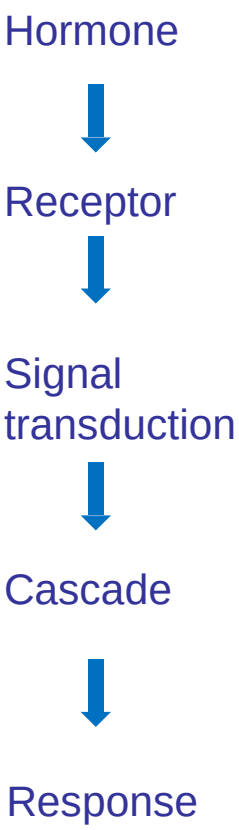
VETS30015 / VETS90121

Intended learning objectives

1. **For each of the following structural hormone groups**
    1. Peptides (eg insulin),
    2. Catecholamine (eg adrenalin)
    3. Thyroid hormones (eg thyroxine)
    4. Eicosanoids (eg prostaglandin) and
    5. Steroids eg cortisol
- **Describe:**
    - How and where the hormone is produced
    - The hormone's main biological function(s)
    - How the hormone's secretion is regulated
2. Describe using specific hormone examples, how negative and positive feedback process work.
3. Explain using examples, how certain diseases can interfere with the production or effect of a hormone

Chemical classes of hormones

- 1) Peptides: chains of specific amino acids
  - Hypothalamus, pituitary, pancreas, parathyroid gland, kidneys, liver, heart, & GI tract.
    - Insulin, vasopressin, TSH, calcitonin etc
- 2) Amines: Tyrosine derivatives
  - a) Catecholamines (Adrenal Medulla)
    - Adrenalin & noradrenalin
  - b) Thyroid hormones
    - Thyroxine & triiodothyronine
- 3) Steroids: Cholesterol derivatives
  - Adrenal cortex, gonads & placental hormones
    - Cortisol, aldosterone, oestrogen, testosterone etc
- 4) Eicosanoids: Arachidonic acid derivatives. Usually act as autocrine or paracrine signalling molecules, but can act distally
  - There are four families of eicosanoids—the prostaglandins, prostacyclins, the thromboxanes and the leukotrienes



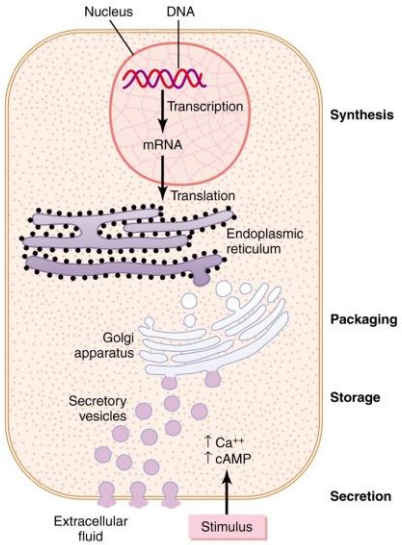
Protein or peptide hormones

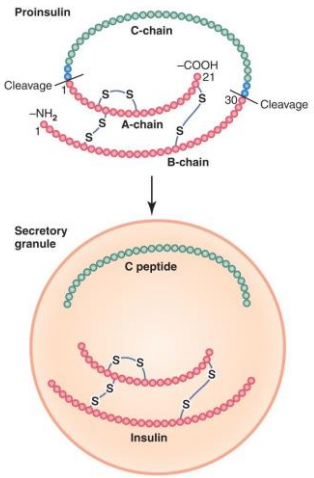
1. Hormone formation
    - Preprohormones (rough endoplasmic reticulum) –——> prohormones ——> active hormones
    - Golgi complex concentrates the finished hormones and they are stored in secretory vesicles.
    - Appropriate stimulus usually Ca2+ results in exocytosis.
1. Peptides (hydrophilic) are transported as free hormone dissolved in the plasma.
2. Bind to specific cell surface receptor on target cell
    - Activates second messenger ---> cascade effect

Prohormone cleavage – insulin

Proinsulin is cleaved to form the connecting peptide (C peptide) and insulin (α and β chains)

Packaged in secretory granules





Guyton & Hall, 2011

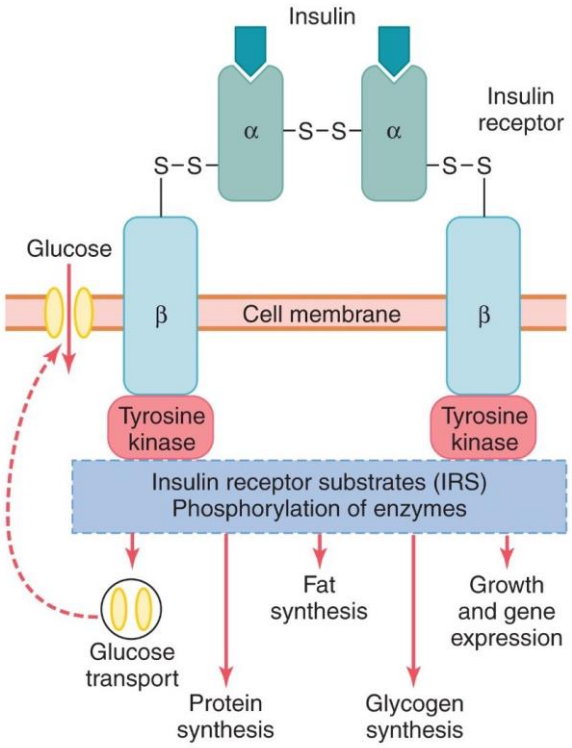
Peptide Hormones

Solubility:	Hydrophilic (polar)
Synthesis:	Rough ER, Packaged in Golgi complex
Storage:	Secretory granules
Secretion:	Exocytosis
Transport:	Free hormone: soluble
Receptor site:	Surface of target cell
Action:	Ion channel changes or Second messenger system

Insulin

- Anabolic hormone produced in the pancreatic β cells in times of excess nutrient availability
  - Allows the body to use carbohydrates as energy sources and store nutrients
- Targets
  - Liver, muscle, adipose tissue
- Functions
  - Lowers blood glucose levels
  - Increases facilitated diffusion of glucose into cells
  - Increases conversion of glucose into glycogen (glycogenesis)
  - Increases uptake of amino acids and protein synthesis
  - Increases synthesis of fatty acids (lipogenesis)
  - Slows glycogenolysis
  - Slows gluconeogenesis
- Insulin receptor
  - Example of enzyme-linked receptor (tyrosine kinase)
  - Tyrosine phosphorylation triggers multiple pathways

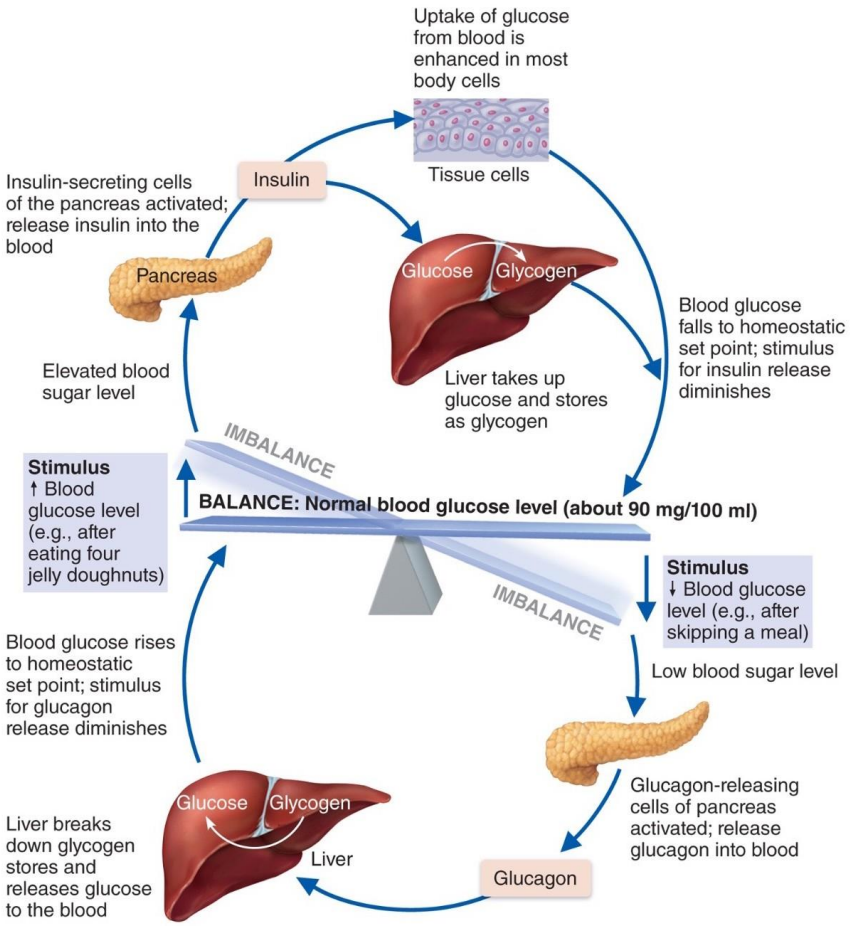
Insulin receptor



Guyton & Hall, 2011

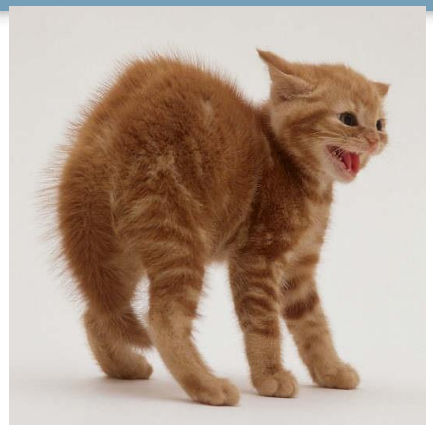
Regulation of insulin secretion

- Glucose is most important regulator of insulin secretion
- Factors controlling insulin secretion
  - -β cells monitor levels of circulating metabolites
    - Glucose
    - Leucine & alanine
      - Amino acids have little effect in absence of glucose increase, but they double insulin release in combination with glucose
  - Neuronal & hormonal
    - Parasympathetic stimulation
    - CCK (cholecystokinin)
    - Gastric hormones stimulate an 'Anticipatory' release of insulin
    - Other hormones, eg glucagon, growth hormone, cortisol

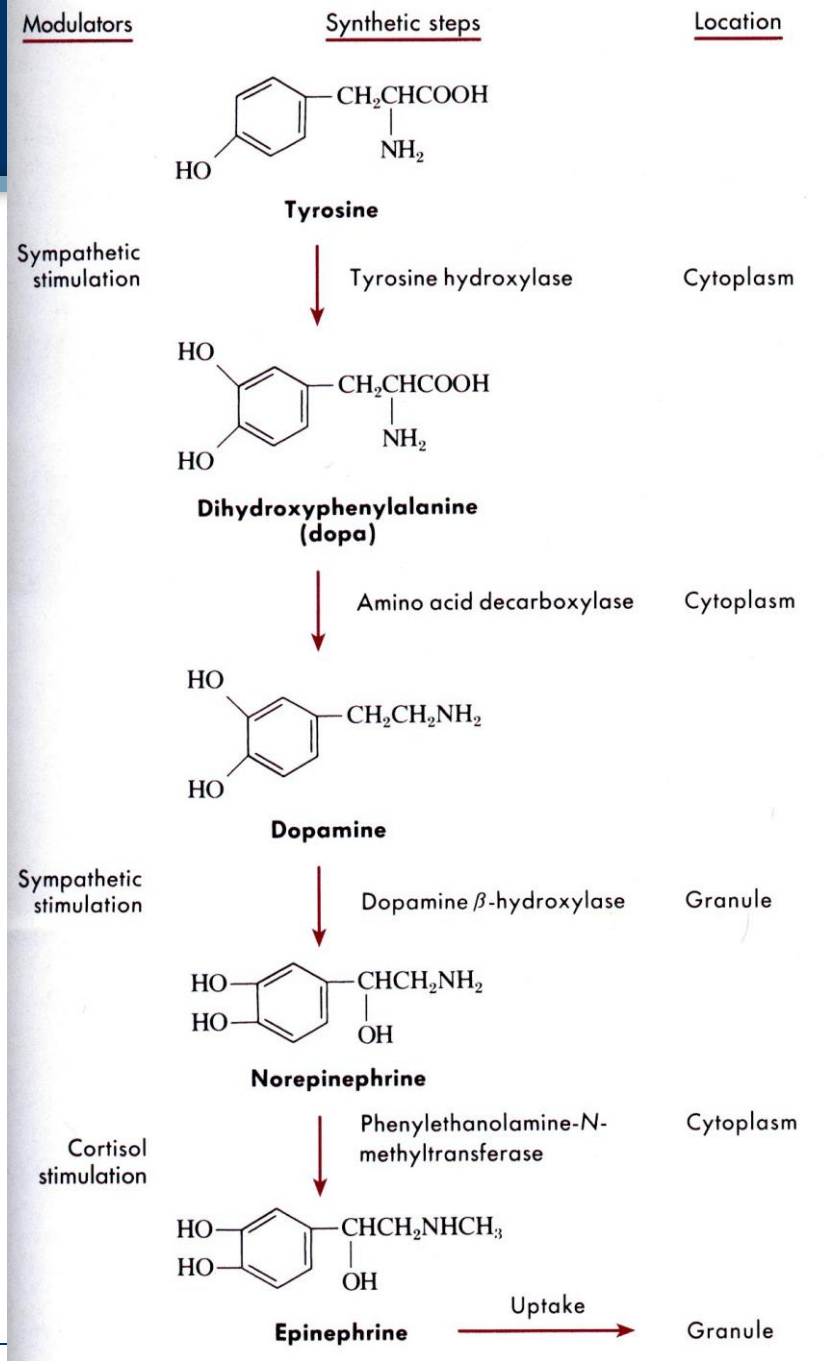


Source : Marieb, 2012

Regulation of catecholamines



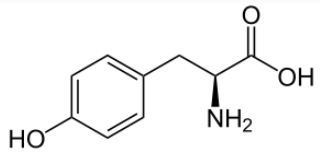
- Stress is the major stimulation of adrenalin or epinephrine release
  - Threat, noise, excitement, high temperature
- The catecholamines are synthesised in sequence from tyrosine
- No negative feedback loop. Action is stopped mainly by degradation as hormones have a short ½ life



Berne and Levy Principles of physiology 1996

Amine Hormones: Catecholamines (dopamine, adrenaline and noradrenaline)

- Derived from tyrosine
- Catecholamines – synthesized in adrenal gland and stored in preformed vesicles
- [Thyroid hormones – special case and covered separately]

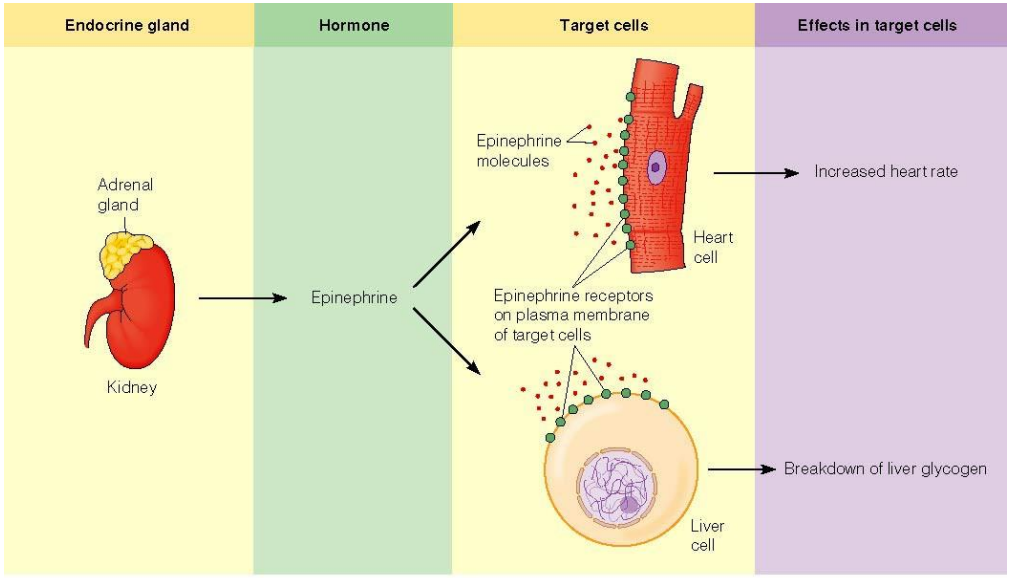


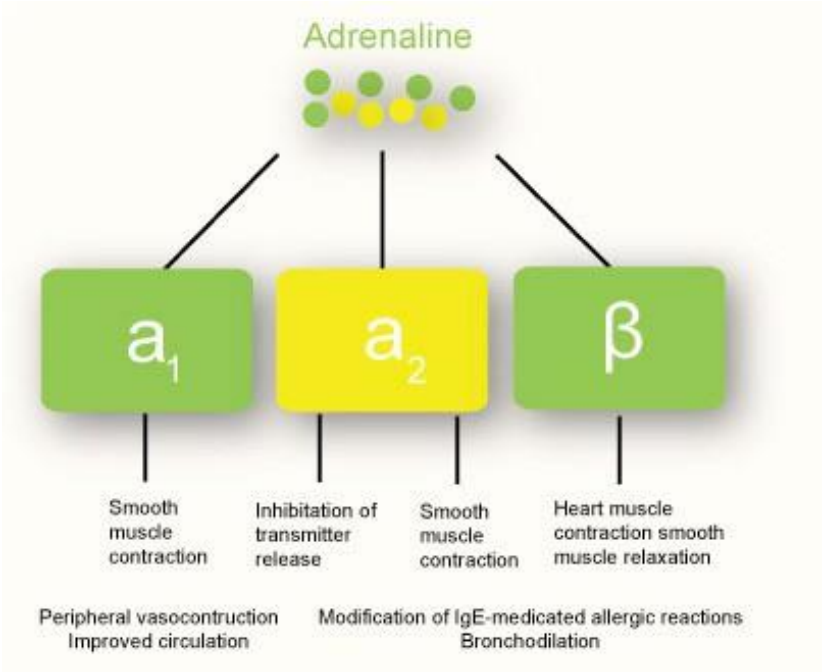
Tyrosine

Structure:	Tyrosine Derivative
Solubility:	Hydrophilic
Synthesis:	Cytosol
Storage:	Secretory (Chromaffin) Granules
Secretion:	Exocytosis
Transport:	As a Free Hormone and Bound to Plasma Proteins
Receptor site:	Surface of Target Cell
Action:	Second Messenger System

Amine Hormones: Catecholamines (dopamine, adrenaline and noradrenaline)

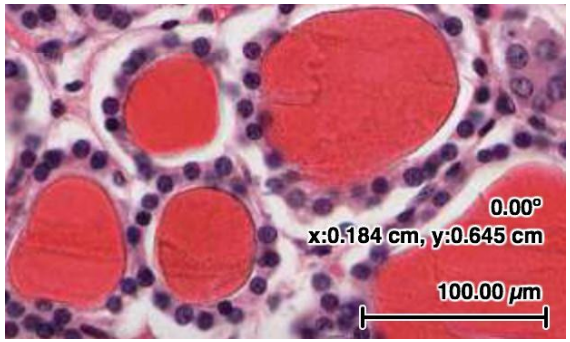
- Adrenaline (Epinephrine)
- Produced in adrenal medulla following sympathetic stimulation
- Response depends on the receptor in the target tissue

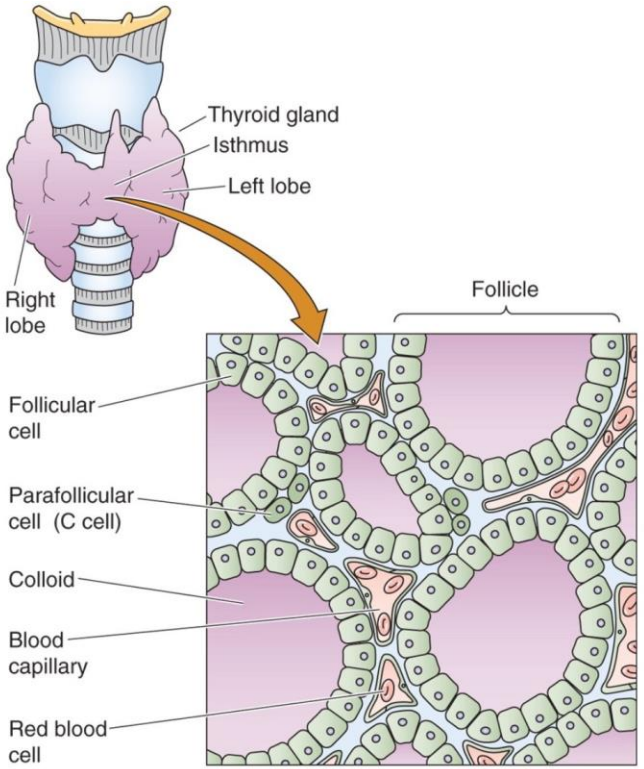




Amine hormones: Thyroid hormones

- Lipophilic amines, but polarity of the iodine means active transport is required across cell membranes
- Produced in thyroid
- Regulate basal metabolic rate
- Stored as thyroglobulin in colloid follicles
- Cleaved to form pro-hormone Thyroxine (T4) & active Triiodothyronine (T3)

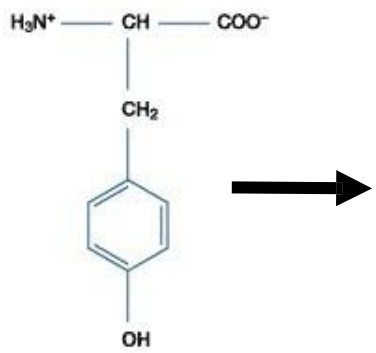




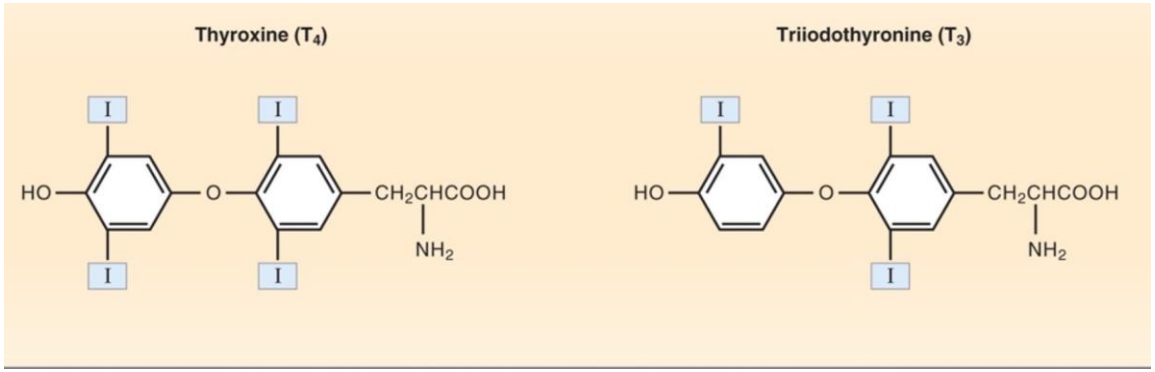
Boron & Boulpaep 2nd ed 2012

Thyroid hormones – tyrosine-derived

Tyrosine



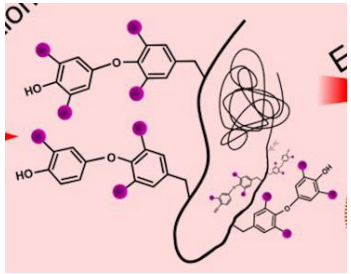
- Thyroxine (T4) & Triiodothyronine (T3)
  - Iodinated forms of tyrosine derivatives.



Pronunciation

Thyroxine: thi-rok-sin
Triiodothyronine: tri-i-o-do-thi-ro-nēn

Stored as thyroglobulin

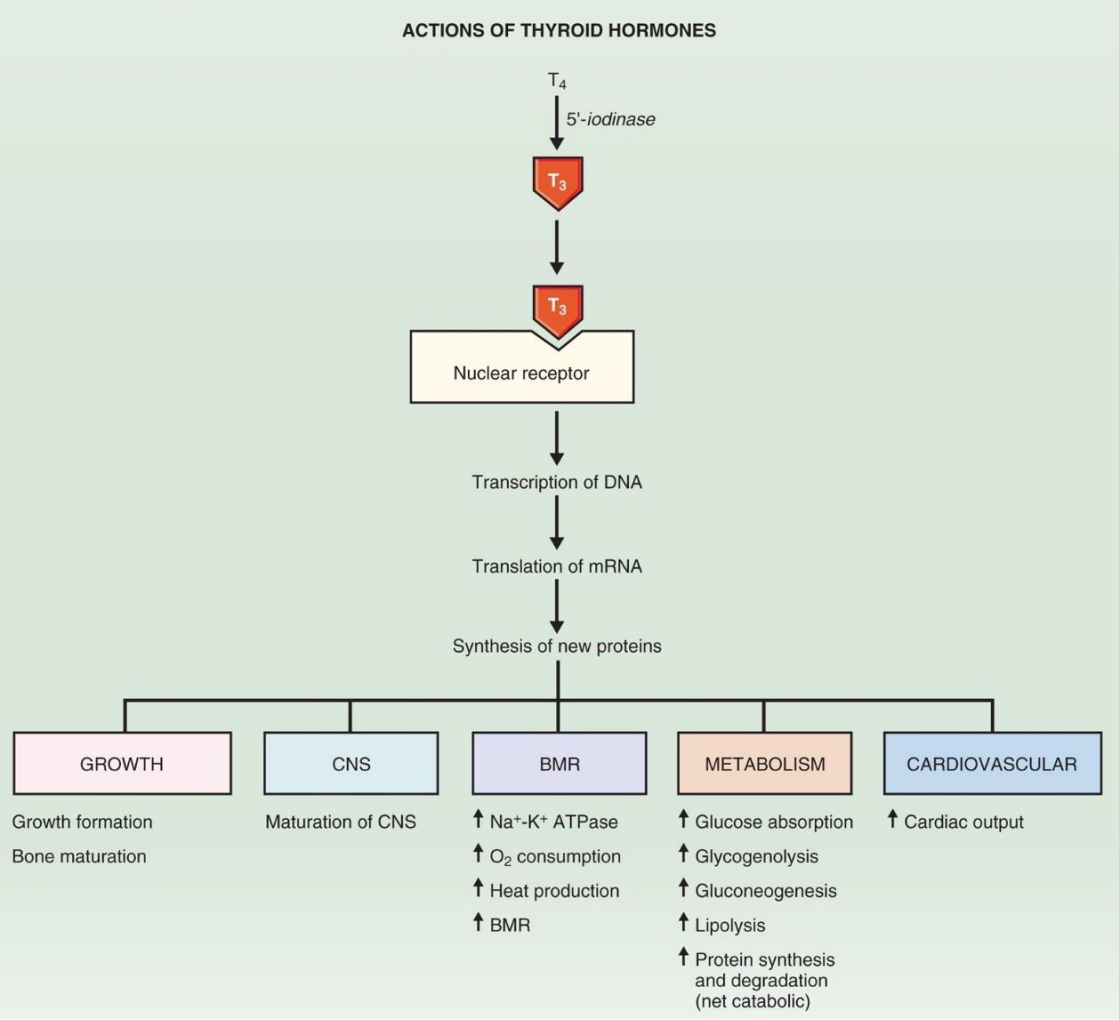


Sources : www.brinkmanncanada.com;Marieb, 2012; Häggström, Mikael

Amine Hormones: thyroid hormones

Structure:	Tyrosine and Iodine Derivative
Solubility:	Lypophilic, but now known to be actively transported into cells by transporters (ATP-dependent carriers)
Synthesis:	Within large glycoprotein (thyroglobulin)
Storage:	Stored as thyroglobulin in colloid follicles
Secretion:	Exocytosis
Transport:	Mostly bound to Plasma Proteins (thyroxin-binding globulin)
Receptor site:	Inside Target Cell
Action:	Direct effect on genes

Metabolic actions of thyroid hormones



- Thyroid hormone effects
  1. Increased metabolic rate
  2. Increased oxygen consumption by mitochondria
  3. Nutrients
  4. Thermogenesis

Regulation of T3 & T4 secretion

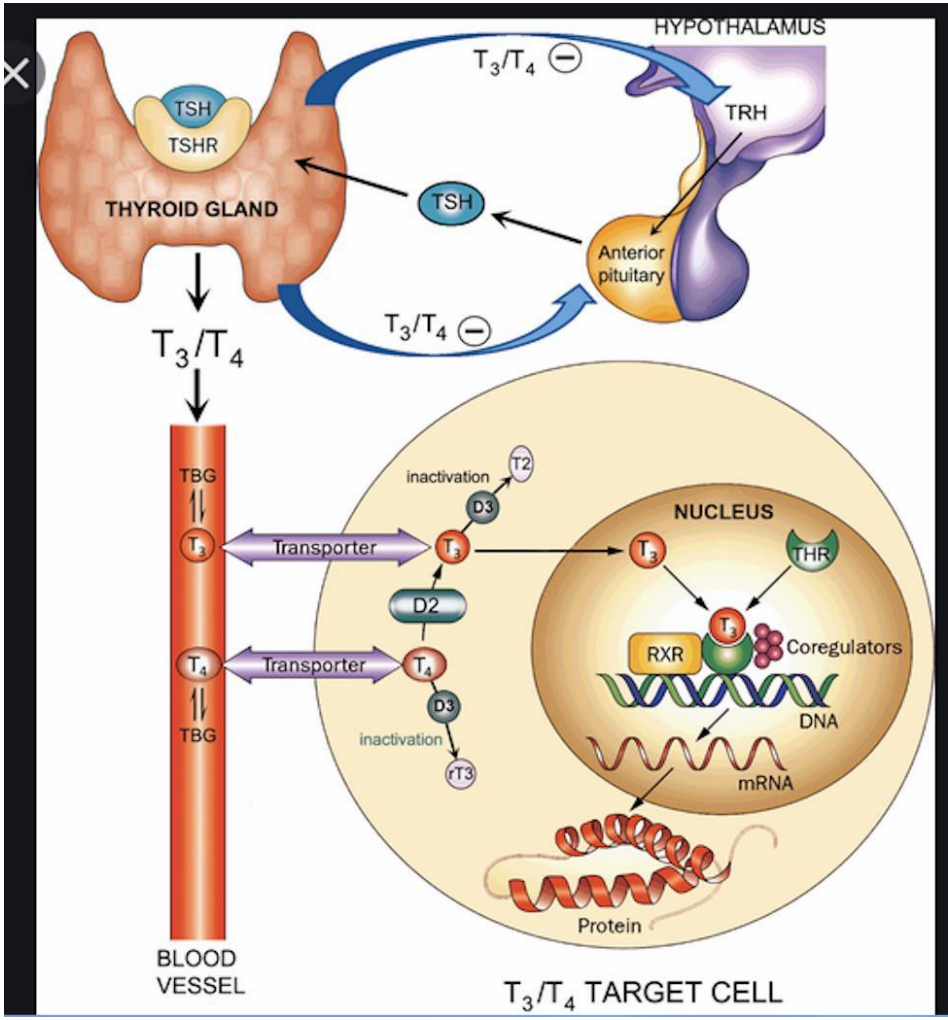
Thyrotropin releasing hormone (TRH)

- formed in hypothalamus

  Response to blood levels T4/T3

- TRH is released into portal veins of hypothalamic-hypophyseal tract
- Stimulates thyrotropes to release TSH into blood
- TSH stimulates follicular thyroid cells to produce and secrete T3 & T4

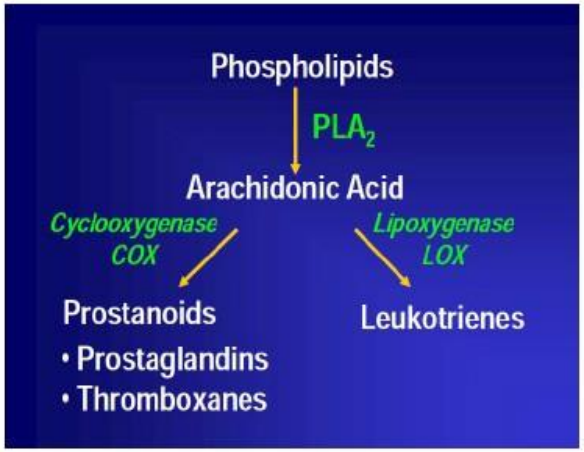
As levels of T3/T4 rise, negative feed back loops reduce synthesis of TRH in hypothalamus (long arm) and release of TSH in the anterior pituitary (short arm)

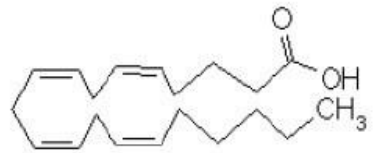


Eicosanoids

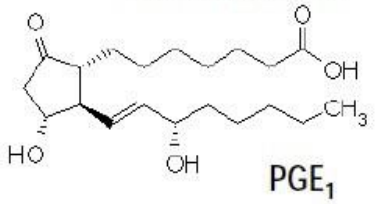
- 20 carbon containing compounds
- Many different prostaglandins and other bioactive products derived from arachidonic acid.
- **Prostaglandins**
- **Thromboxanes** } [Prostanoids]
- **Leukotrienes**

- Prostaglandins produced by most cells
- Eicosanoids not stored by cells- produced on demand





arachidonic acid



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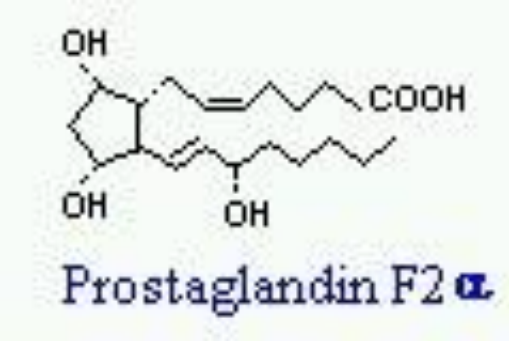
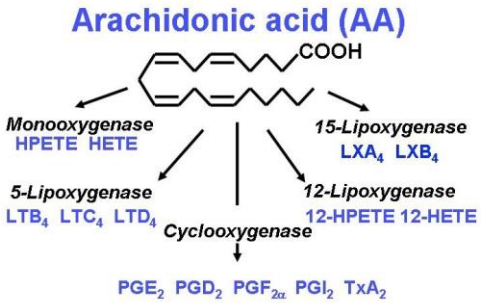
Functions of Eicosanoids



Phospholipids in membrane



Arachidonic acid

Prostaglandins

- vasodilators
- regulate blood flow

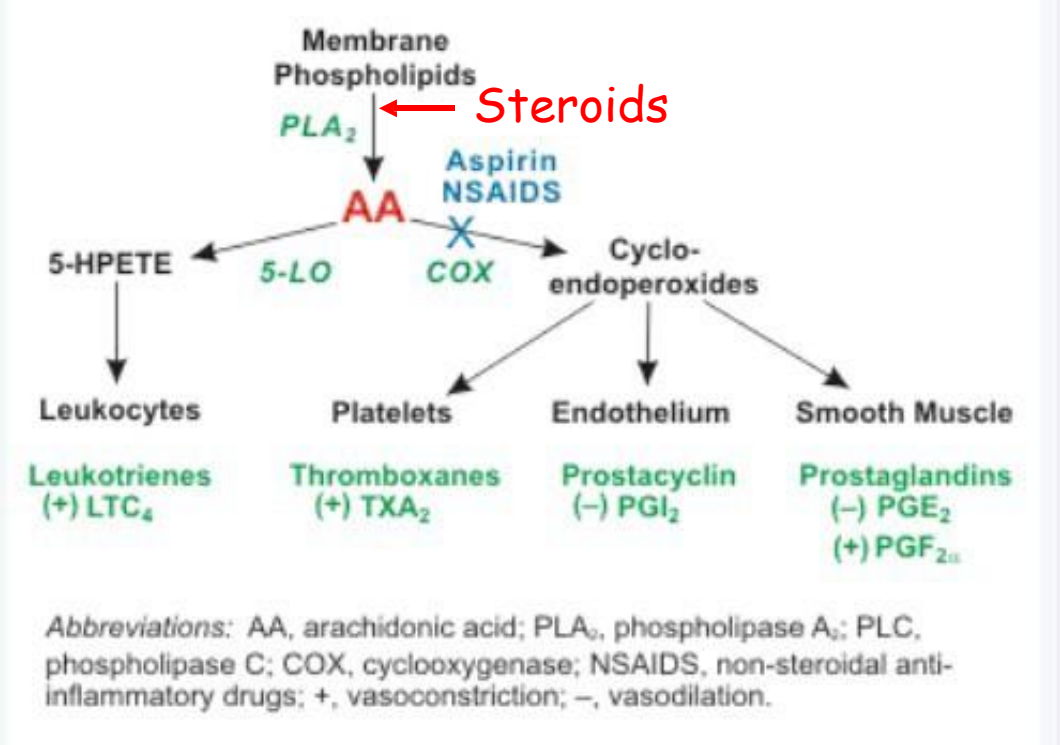
Thromboxane A2

- induces platelet aggregation
- promotes vasoconstriction

Leukotrienes

- allergy involvement
- neutrophil chemo-attractant
- vascular permeability

Drug affects on Eicosanoids

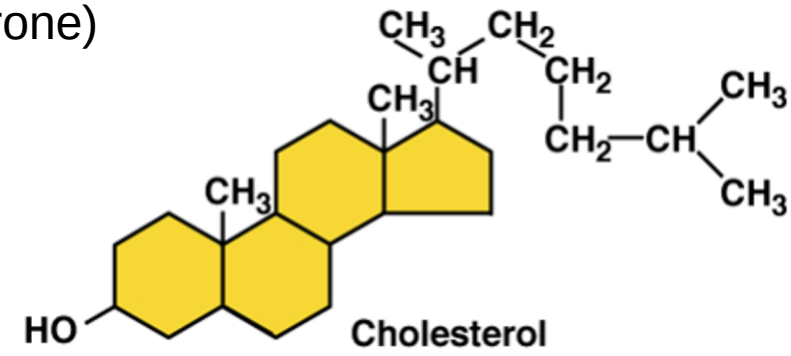


https://www.cvphysiology.com/Blood%20Flow/BF013

Steroid hormones

1) adrenal cortex (cortisol, androgens & aldosterone)
2) ovaries (estrogen and progesterone)
3) testes (testosterone
4) placenta (estrogen and progesterone)

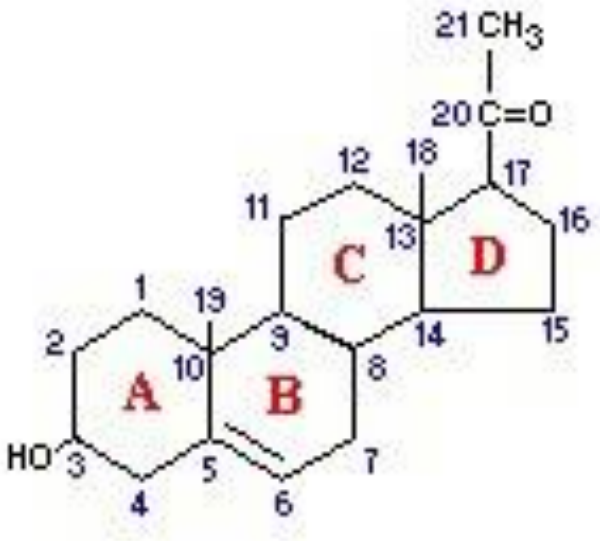
Cholesterol derivative obtained from low density lipoproteins



Cholesterol

Stored (or its derivatives) in lipid droplets within each steroidogenic organ.

- Produced through a series of enzymatic reactions
- Cholesterol to pregnenolone
    - (rate limiting step).
- Each steroidogenic organ can produce only those steroid hormones for which it has a complete set of enzymes.

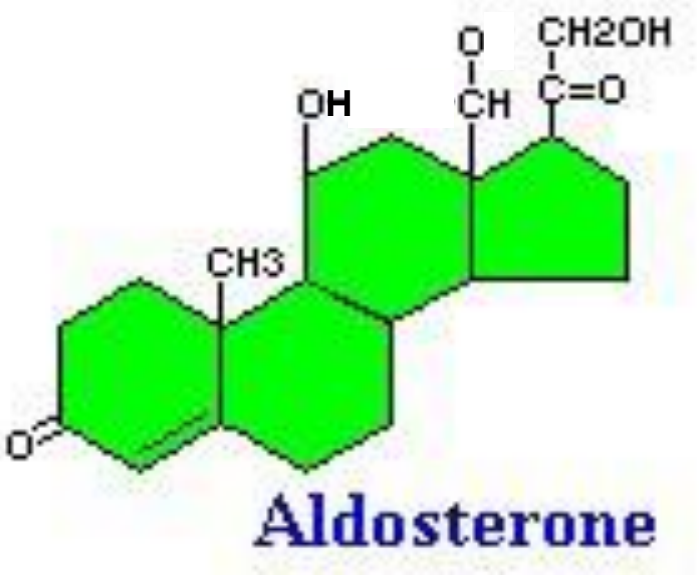


Pregnenolone

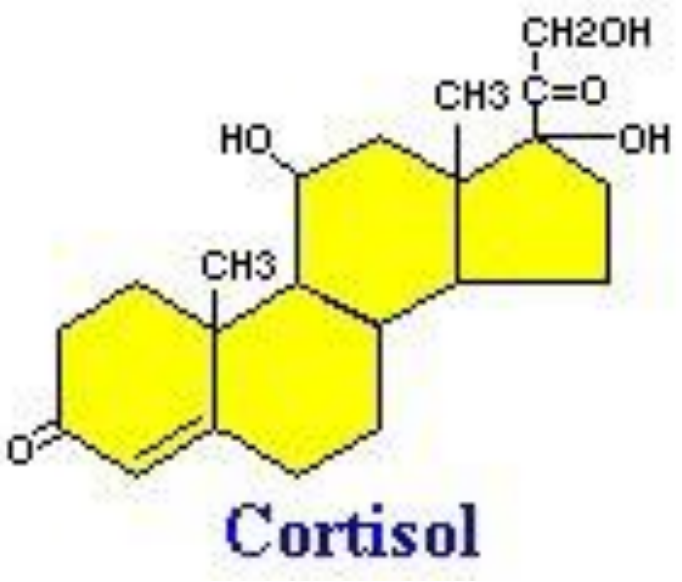
Cyclo pentano perhydro phenanthrene

Steroid hormone structure

- Mineralcorticoid
  - Regulates Na/K balance



Aldosterone



Cortisol

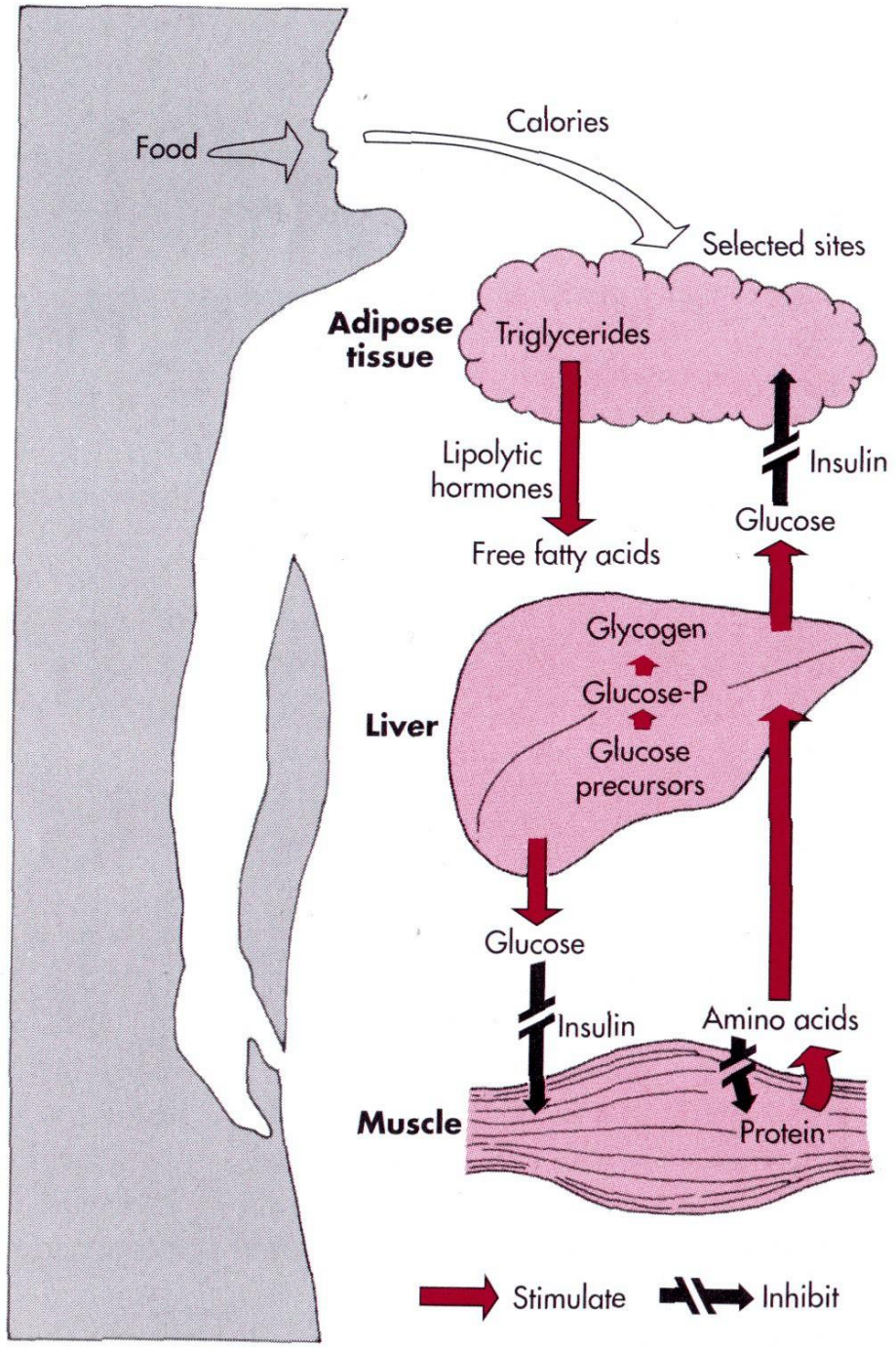
- Glucocorticoid
  - Glucose homeostasis

arbl.cvmbs.colostate.edu/hbooks/pathphys/endocrine/basics/chem.html

Steroids

Solubility:	Lipophilic
Synthesis:	Stepwise Modification of Cholesterol Molecule in Various Intracellular Compartments (in the Endocrine Gland and Also in Target Tissues)
Storage:	Hormones Not Stored, Only Precursor (Cholesterol) Stored
Secretion:	Diffusion
Transport:	Mostly Bound to Plasma Proteins
Receptor site:	Inside of Target Cell
Action:	Direct Effects on Genes → Production of New Proteins

Cortisol



Metabolic Actions Corticosteroids

Maintains blood glucose levels during fasting & increases blood glucose during stress

1. Early fasting - defence against hypoglycaemia.
   - Increase plasma glucose
   - Liver Increased glucose output
   - Promotes gluconeogenesis, glycogenolysis & lipolysis
2. Late fasting stage
   - build up of glycogen stores

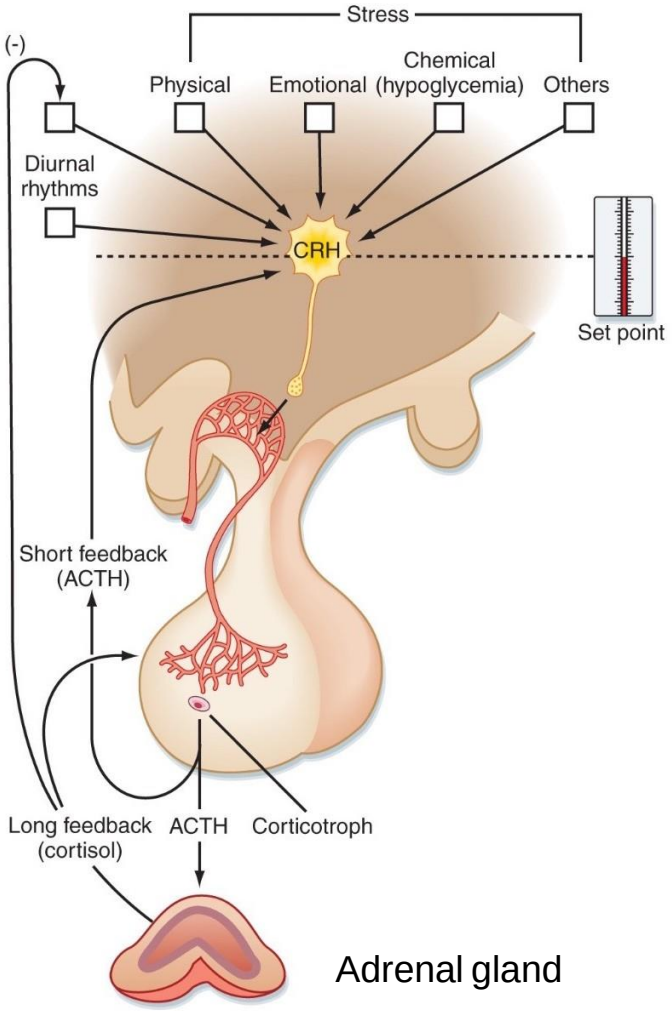
Anti-inflammatory actions

Inhibits arachidonic acid production and prostaglandins

Berne & Levy Principles of Physiology 1996

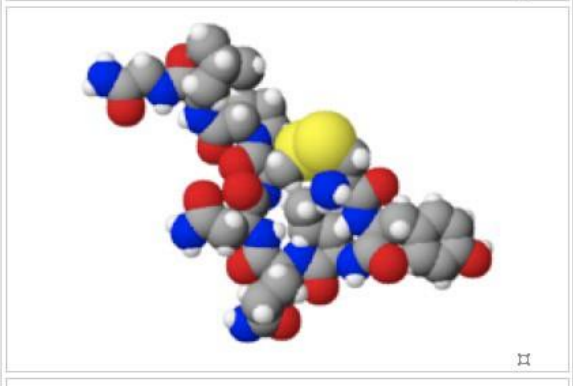
Regulation

- Negative feedback regulation
  - pituitary and hypothalamus by cortisol
    - Long feedback loop
  - on hypothalamus by ACTH
    - Short feedback loop



Berne & Levy 2018

Oxytocin



- Peptide hormone (9 aa)
  - Produced in supraoptic and paraventricular nuclei
  - Also acts as a neurotransmitter in brain
- Released by posterior pituitary
  - Oxytocin receptors are on smooth muscle cells
    - mammary gland and uterus

1. Promotes milk ejection (milk let down) during lactation

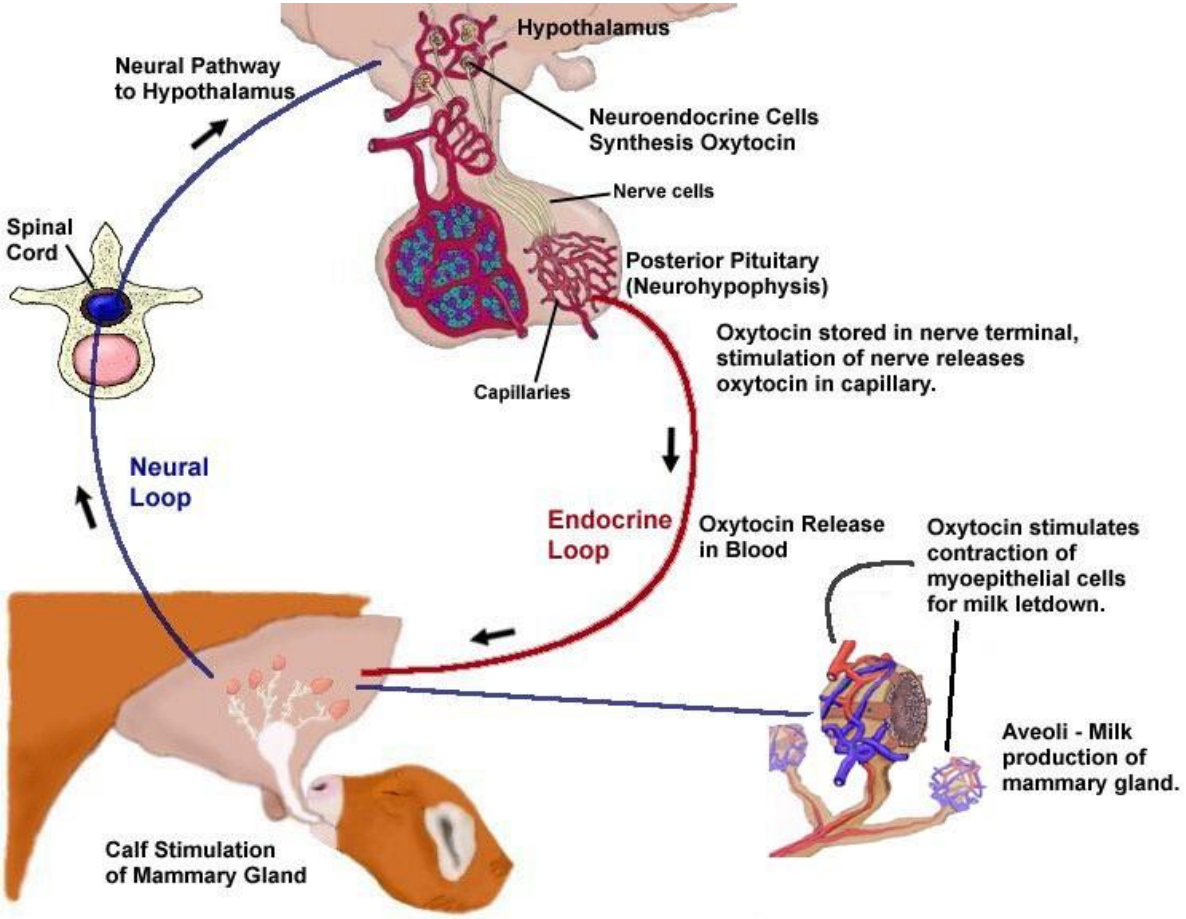
- Milk initially secreted into alveoli (sacs) within mammary gland
- OCT stimulates contraction of myoepithelial cells (smooth muscle cells) which surround alveoli

2. Uterine contraction during parturition

- Important in cervical dilation & uterine contractions
- After birth maintains haemostasis & evacuation of placenta

$C_{43}H_{66}N_{12}O_{12}S_2$

Positive Regulation of Oxytocin Secretion



1. Suckling
   - Neurogenic reflex to hypothalamus
2. Pregnancy and Parturition
   - Oxytocin receptors in uterus increase late trimester & during labour
   - Estrogen induced
   - Uterus stretching ---> more oxytocin released

www.ansi.okstate.edu-course-3443-study-Notes-endocrin-oxytocin.jpg.

Basis of endocrine disorders leading to disease

- Increased or reduced hormone activity:
  - Tumours
    - Hyperthyroidism due to thyroid tumour – increased T3 & T4
    - Increased cortisol due to benign pituitary tumour – Cushing's disease
  - Immunological causes
    - Grave's disease – autoimmune hyperthyroidism
    - Type I diabetes – autoimmune destruction of pancreatic islet cells
  - Genetic disorder (absence of enzyme)
  - Dietary deficiency
    - Hypothyroidism due to insufficient iodine
- Increased removal from the blood or transport deficiencies
    - Liver disease – reduced plasma protein binding
- Transduction failure – adequate hormone, but target cells don't respond
    - Receptor deficiency or disorders of signalling pathway - transduction

Diabetes Mellitus : clinical correlations

from Cunningham Veterinary Physiology

History

- You are presented with a 10-year-old, intact, female poodle whose owner is upset because the dog urinates in the house.
- In addition, the owner has noticed that the animal drinks larger amounts of water than it has in the past.
- Although the owner indicates the dog has a good appetite, it appears to have lost weight over the past few months.

Clinical examination

- You are able to run a blood glucose determination in your hospital and tell the owner that the glucose concentration is 14.9 mmol/L
- During the examination you check the dog's breath and detect a sweet odour.
- Among the organ systems you check are the eyes, and you find developing cataract formation.
- Because you have seen this dog many times before, you check its weight and find that it has lost 1 kg since its last admittance a year ago.

Questions:

1. What does insulin normally do in dogs ?
2. Why is the poodle drinking more and urinating in the house?
3. Why has the dog lost weight?
4. What is the sweet odour on the dog's breath and why does it occur?
5. Why has the dog developed a cataract?
6. What is the normal range of glucose in blood ?
7. How do you confirm if the dog has diabetes mellitus?