*Key concepts in Digestion...*

*'Who decided it was bad to be fat' – module 4*

# The endocrine pancreas

## …hormones and blood sugar homeostasis


Professor Barry Campbell

GI Physiology

e-mail: bjcampbl@liv.ac.uk

**http://pcwww.liv.ac.uk/~bjcampbl**



UNIVERSITY OF LIVERPOOL

**Contribution to the following milestone set out for CLC1:**

***FoP2.1(1)*** *identify and describe the common/ serious, extrinsic and intrinsic factors that can affect the normal biological processes in individual organs or organ systems, which could affect the level of oral and general health risk, treatment complications and/or outcomes*

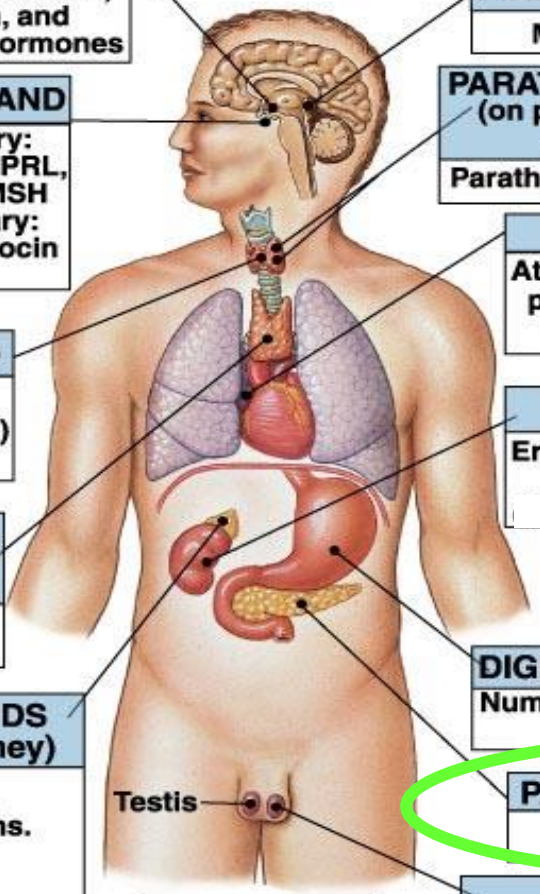
*Every dentist should be aware of the oral manifestations of endocrine disorders!...*

**Objectives:** - To develop an understanding of:

1. **the endocrine system of the human body**
2. **hormones – their discovery, role and secretion**
3. **cellular biology of the endocrine pancreas**
4. **blood sugar homeostasis**
5. **endocrine disorders of the pancreas**

# The endocrine system

*Adapted from Martini - 'Fundamentals of Anatomy and Physiology.'*




**HYPOTHALAMUS**
Production of ADH, oxytocin, and regulatory hormones

*ADH conserves body water*

**PITUITARY GLAND**
Anterior pituitary: ACTH, TSH, GH, PRL, FSH, LH, and MSH
Posterior pituitary: Release of oxytocin and ADH

*GH increases body size*

**THYROID GLAND**
Thyroxine ($T_4$)
Triiodothyronine ($T_3$)
Calcitonin (CT)

*$T_{3/4}$ increase metabolism and growth*

**THYMUS**
(undergoes atrophy during adulthood)
Thymosins

*Maturation of immune system*

**ADRENAL GLANDS**
(one at each kidney)
Each gland contains two endocrine regions.
Medulla:
Epinephrine (E)
Norepinephrine (NE)
Cortex:
Cortisol, corticosterone, aldosterone, androgens

*Fight or flight response (medulla)*

**PINEAL GLAND**
Melatonin

*Induces sleep*

**PARATHYROID GLANDS**
(on posterior surface of thyroid gland)
Parathyroid hormone (PTH)

*Increases blood calcium*

**HEART**
Atrial natriuretic peptide (ANP)

*Decreases blood pressure*

**KIDNEY**
Erythropoietin (EPO)
Calcitriol

*EPO Increases red blood cell formation*

**DIGESTIVE TRACT**
Numerous hormones

*Gastrin regulates acid secretion*

**PANCREATIC ISLETS**
Insulin, glucagon

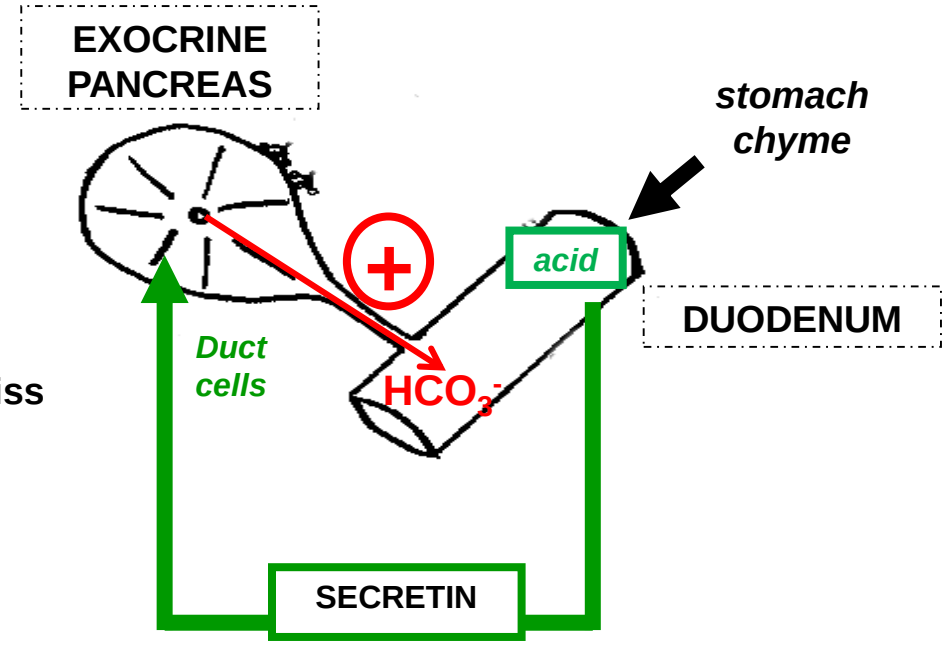
*Blood sugar regulation*

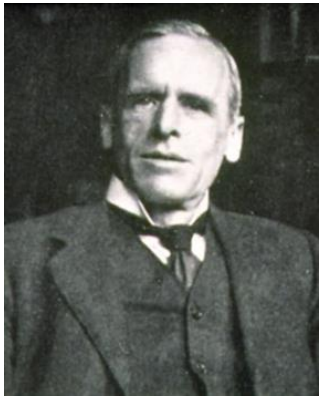
**GONADS**
Testes (male):
Androgens (especially testosterone), inhibin
Ovaries:
Estrogens, progestins, inhibin

*Sexual characteristics*

# What are hormones?

Sir William Maddock Bayliss



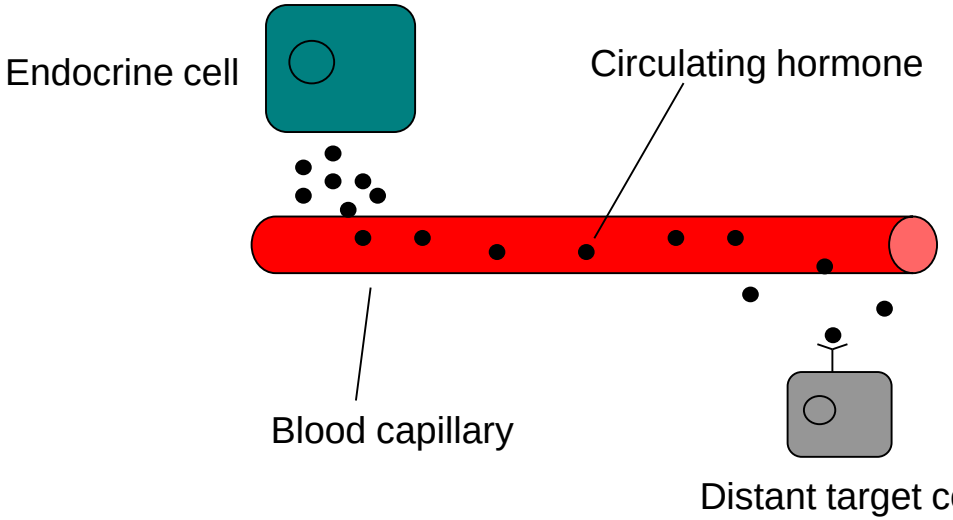
Ernest Henry Starling

Ernest Henry Starling introduced the term 'hormone' in his Croonian Lectures to the Royal College of Physicians, delivered on the 20th, 22nd, 27th and 29th June 1905.

"Hormone" comes from the Greek word hormao - to spur or urge on/to arouse to activity.

# Hormonal and local communication

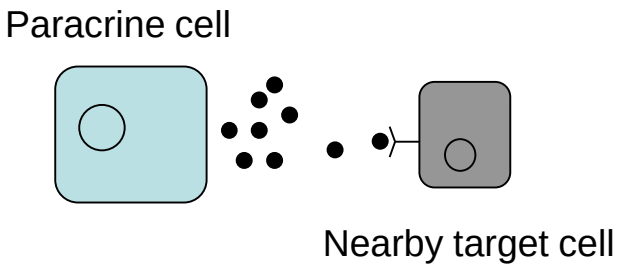
## Endocrine



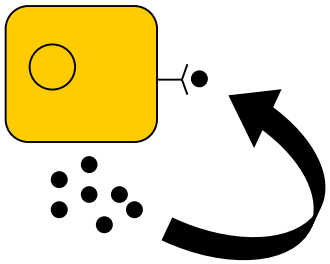

- *Classical **endocrine** hormones are: substances released from one tissue and transported via the bloodstream to a different tissue, resulting in changes to that tissue*

- *Local hormones are not transported via blood*

## Paracrine

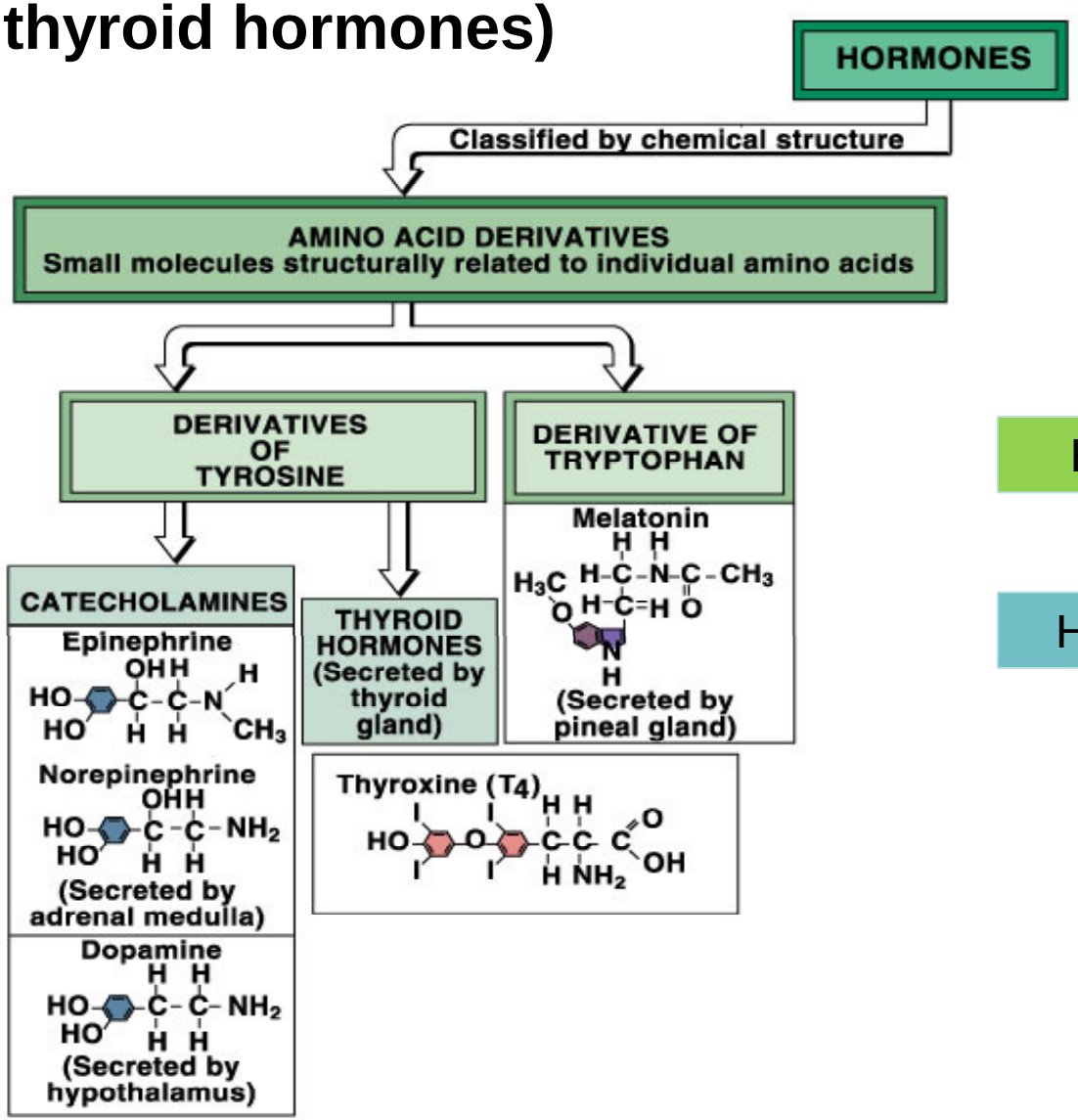



## Autocrine



# Amino acid-derived hormones

**Water soluble, cannot passively diffuse across membranes (except for thyroid hormones)**



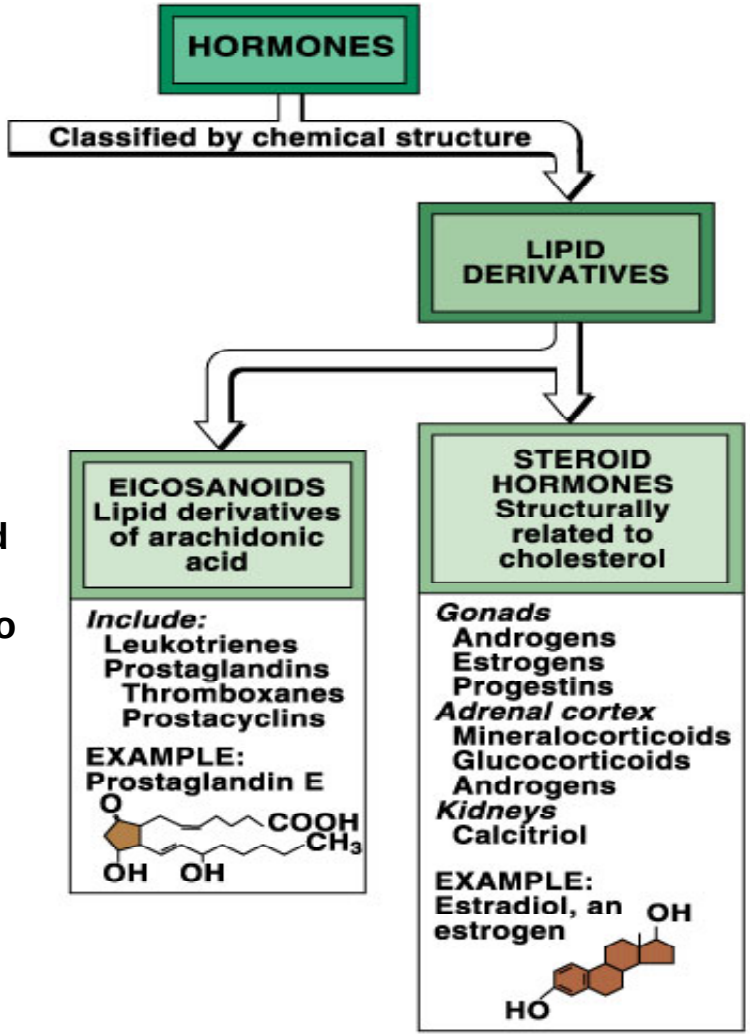

Histidine

↓

Histamine

# Lipid-derived hormones

**Lipid soluble, can passively diffuse across membranes**



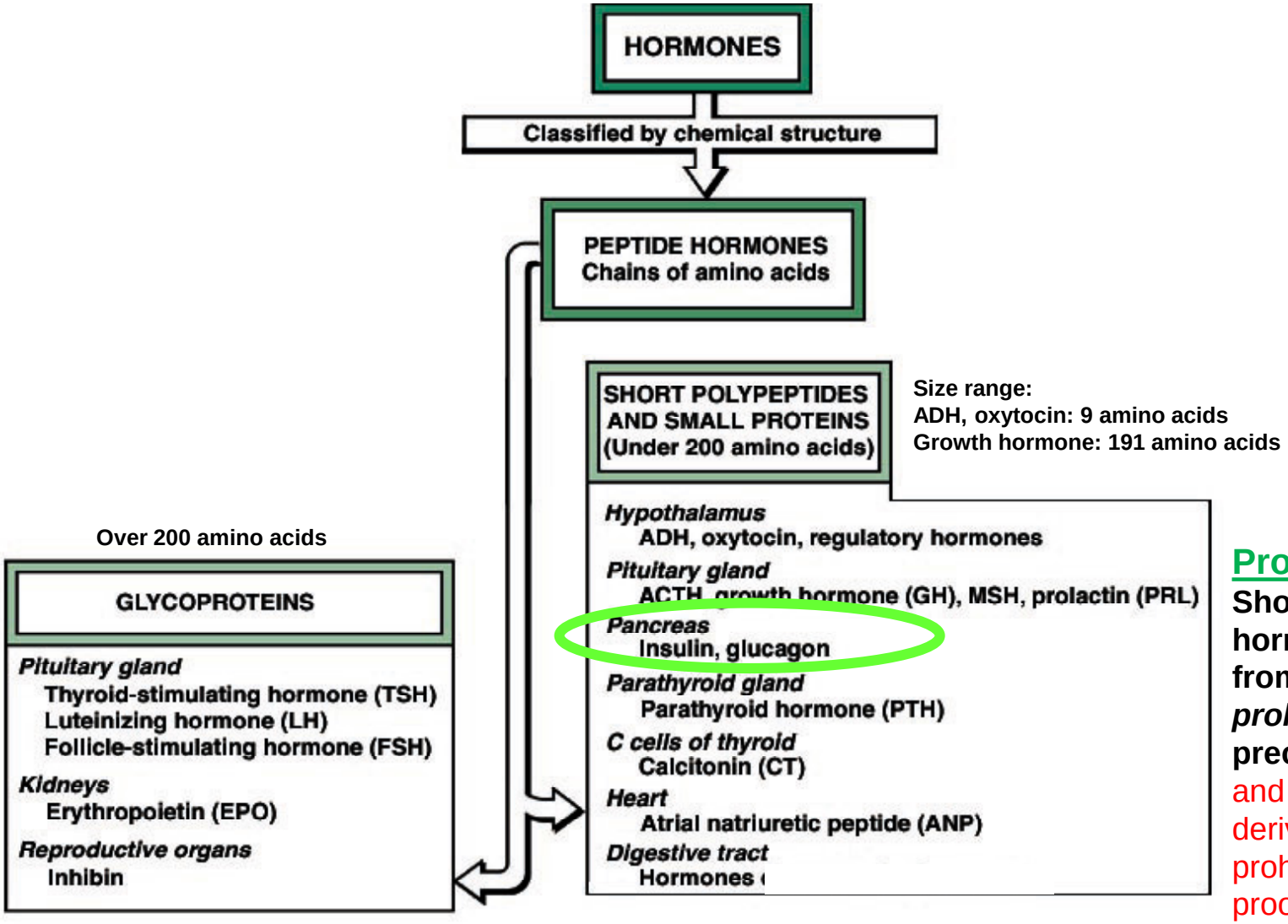

**Arachidonic acid is converted to leukotrienes by lipoxygenase enzymes; and to prostaglandins by cyclooxygenase enzymes (Aspirin is a cyclooxygenase inhibitor)**

**Cholesterol is converted to the various steroid hormones by sequential action of several different enzymes.**

**Androgens (eg. testosterone) are converted into estrogens (eg. estradiol) by enzymatic removal of a single methyl ($CH_3$) group**

# Peptide/protein hormones

## Water soluble, cannot passively diffuse across membranes




**Processing**

**Short polypeptide hormones are derived from larger *prohormone* precursors** (eg., ACTH and αMSH are both derived from the same prohormone, proopiomelanocortin)

# How do endocrine cells synthesise and release hormones?

## Lipid-derived hormones

• not stored in cells, synthesised on demand from precursor lipids

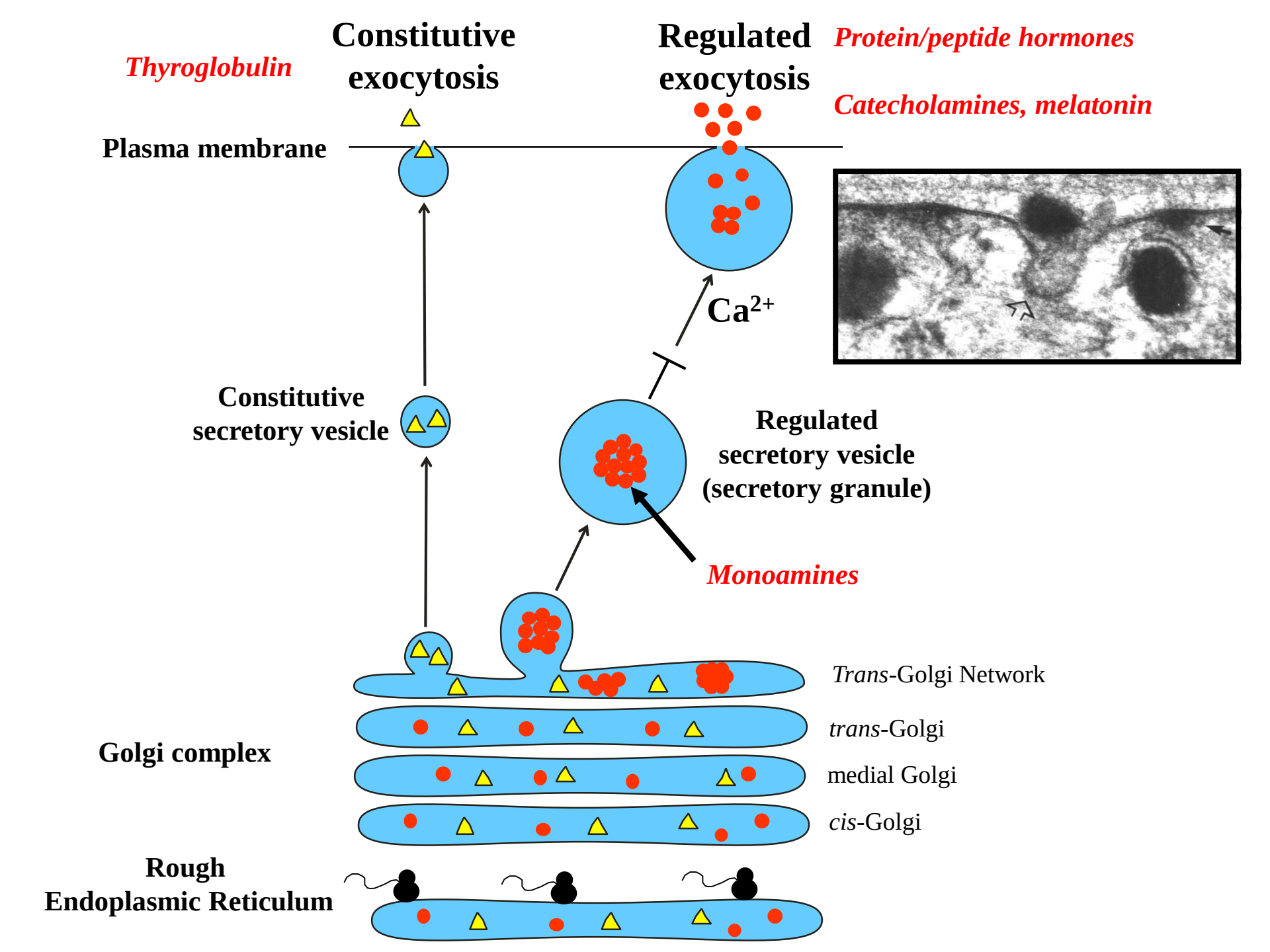
• *Steroid hormones* are formed from cholesterol; first enzymatic modification in mitochondria, remaining modifications in smooth endoplasmic reticulum
- transported in blood bound to serum proteins

• *Eicosanoids* are formed from arachidonic acid in plasma membrane
- once formed, these hormones are released from cells via simple diffusion

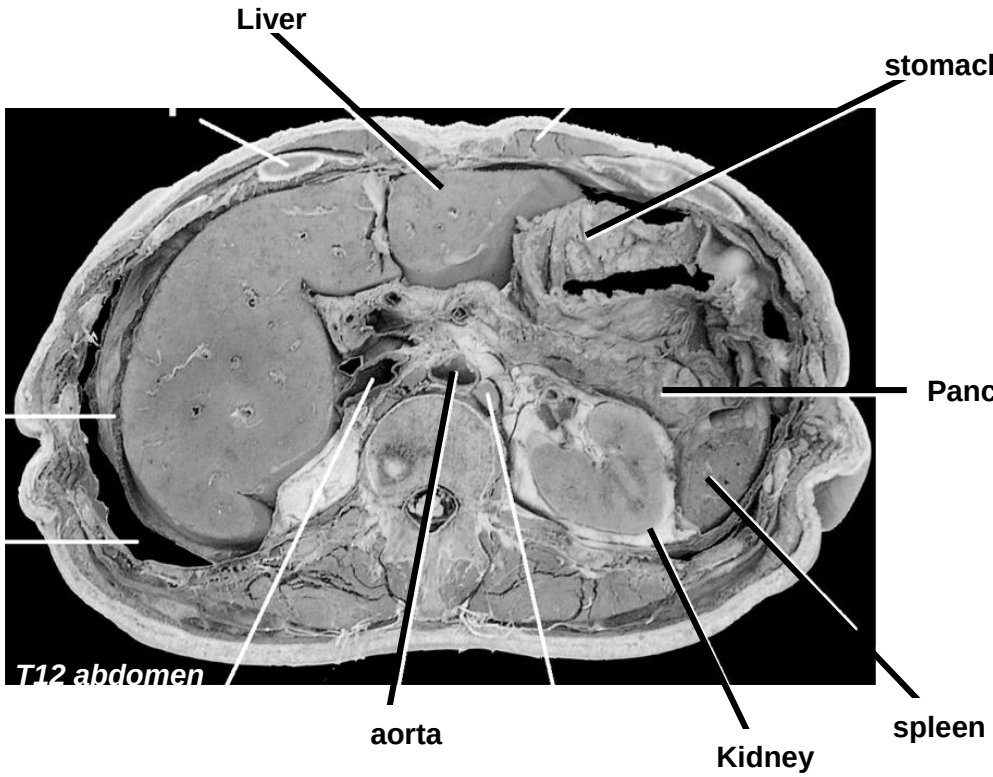
## All other hormones (except thyroid)

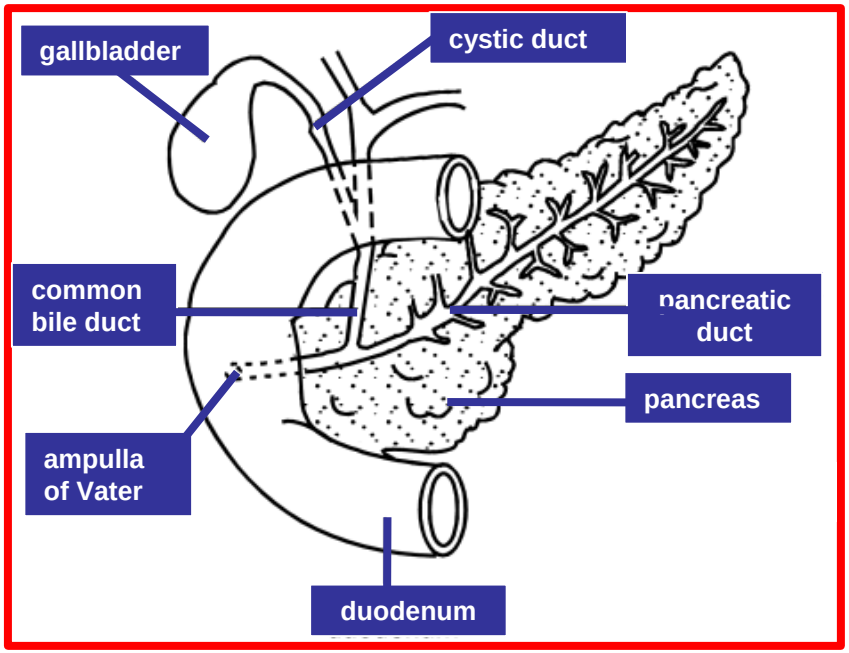
• stored, often at high concentrations, in secretory vesicles

• released by regulated exocytosis when required


Constitutive exocytosis
Regulated exocytosis
Thyroglobulin
Protein/peptide hormones
Catecholamines, melatonin
Plasma membrane
Ca2+
Constitutive secretory vesicle
Regulated secretory vesicle (secretory granule)
Monoamines
Trans-Golgi Network
trans-Golgi
medial Golgi
cis-Golgi
Golgi complex
Rough Endoplasmic Reticulum

# The pancreas



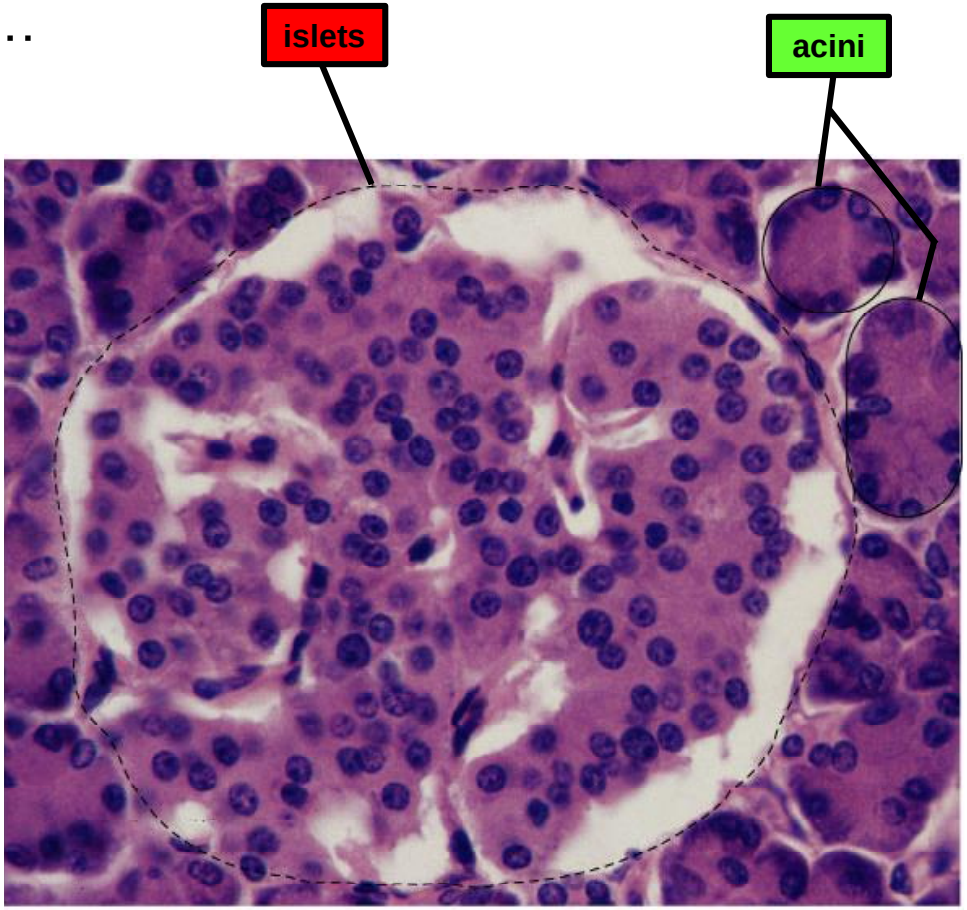
# Pancreatic glands

The pancreas is a mixed gland…

98% exocrine, 2% endocrine

Exocrine cells secrete digestive enzymes and alkaline pancreatic juices into the small intestine

Endocrine cells secrete regulatory hormones.

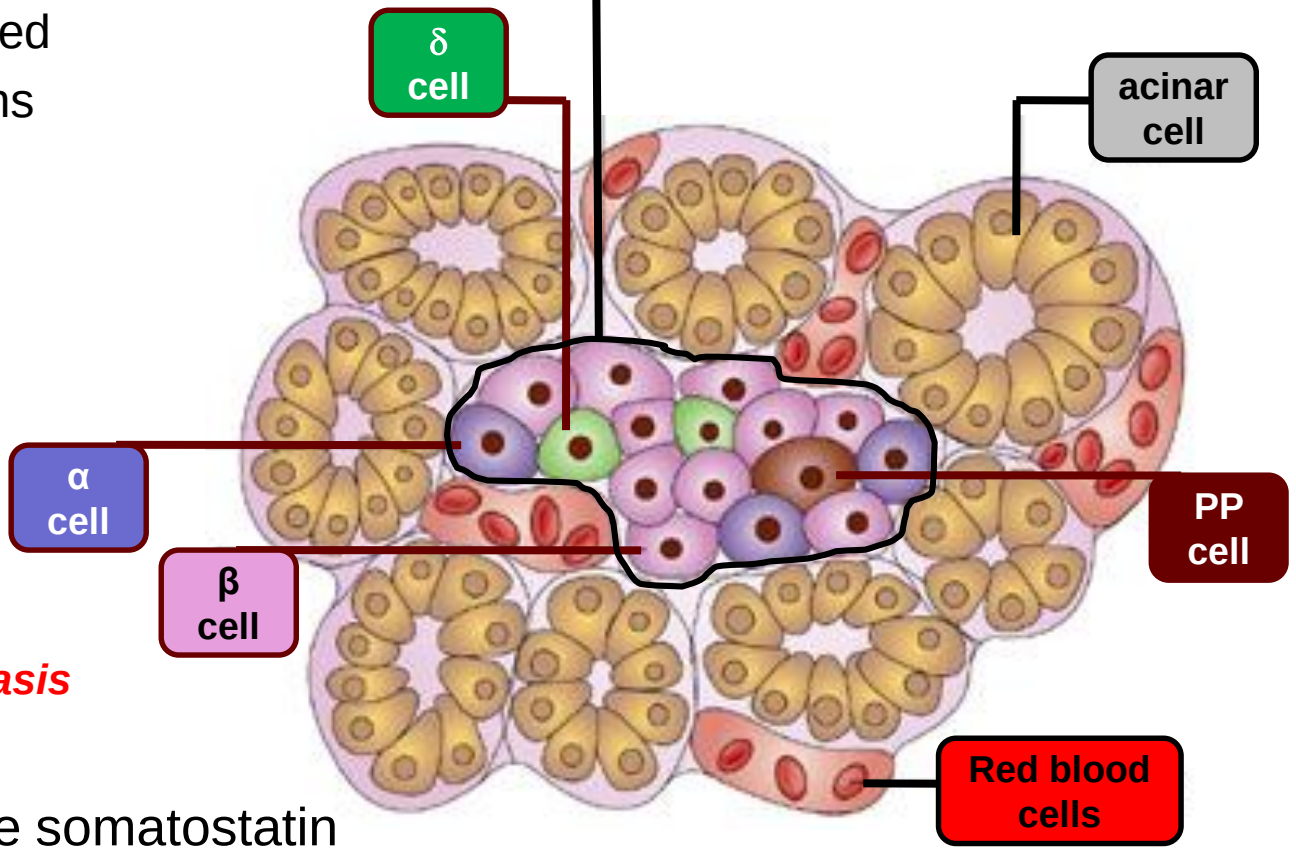



**1869:** Paul Langerhans (Med student, Berlin) discovers a distinct collection of cells within the pancreas. Islets of Langerhans.

**1901:** Eugene Opie discovers that the Islets produce insulin and that the destruction of these cells resulted in diabetes

# Islets of Langerhans

Endocrine cells are located in the islets of Langerhans




**There are 4 cell types:**

- Alpha (α) cells secrete glucagon
- Beta (β) cells secrete insulin

***Control glucose homeostasis***

- Delta (δ) cells secrete somatostatin

***Inhibits insulin and glucagon – paracrine action***

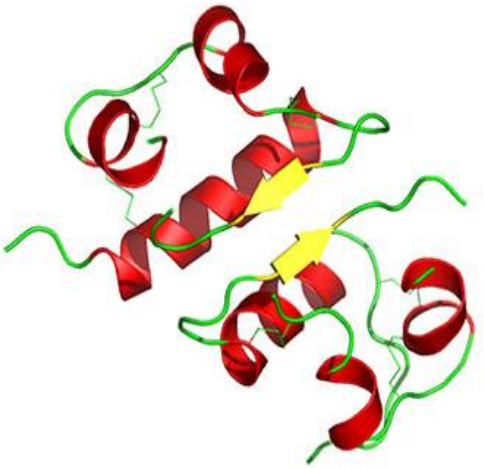
- F or $D_1$ cells secrete pancreatic polypeptide (PP)

***Regulates gastric motility and satiation – inhibiting food intake and stimulating energy expenditure. Also inhibits exocrine pancreas secretions and insulin release***

***Adapted from…Nature Reviews Cancer 2002;* 2, 897-909.**

# Insulin

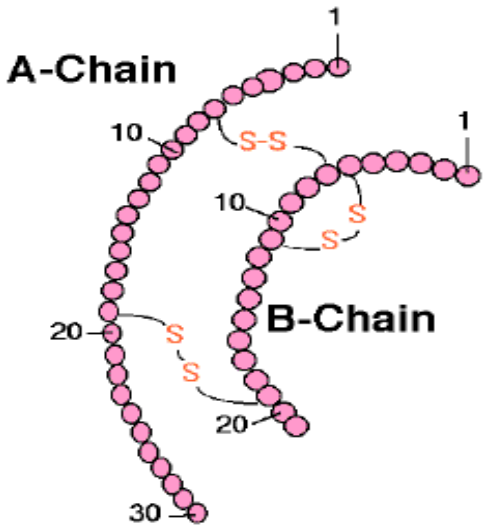
• Insulin is an anabolic hormone, that is, it increases the storage of glucose, fatty acids and amino acids in cells and tissues



• In mammals, insulin is expressed as a single chain prepro hormone, which is secreted through the plasma membrane.

*A prepro- hormone contains extra amino acids not present in the mature hormone*

• Kallikrein, an enzyme present in the islets, aids in the conversion of proinsulin to insulin. The C peptide chain is removed from the proinsulin molecule producing the disulfide-connected A and B chains that are insulin.



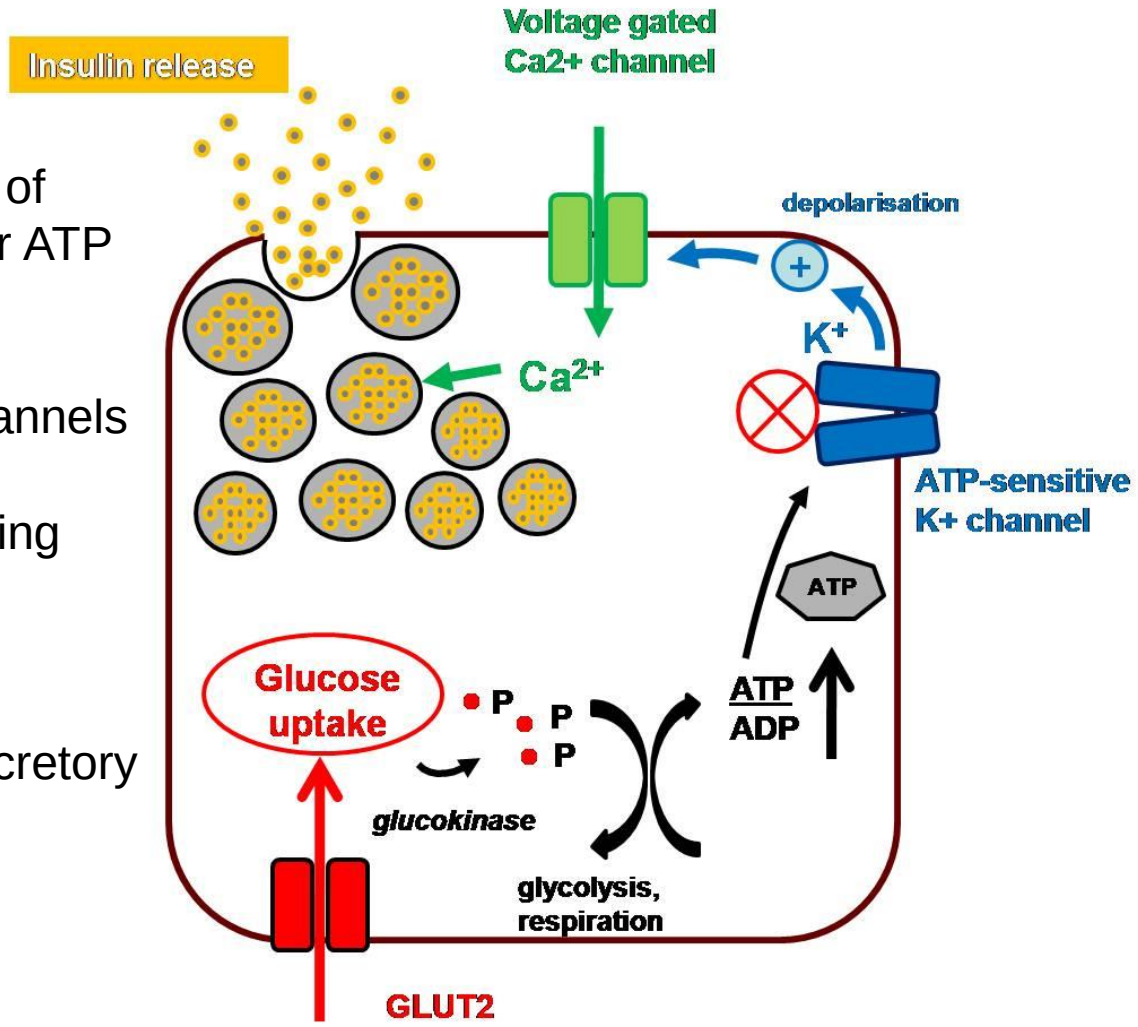

$\alpha$ chain - 30 amino acids long

$\beta$ chain - 21 amino acids long

(If separated they only have partial activity)

# Insulin secretion

- After a meal, increased blood glucose enters β cells
- the glycolytic phosphorylation of glucose causes a rise in cellular ATP
- ATP inactivates potassium channels
- this depolarises the cell, opening calcium channels
- the consequent increase in cytoplasmic calcium causes secretory granule exocytosis

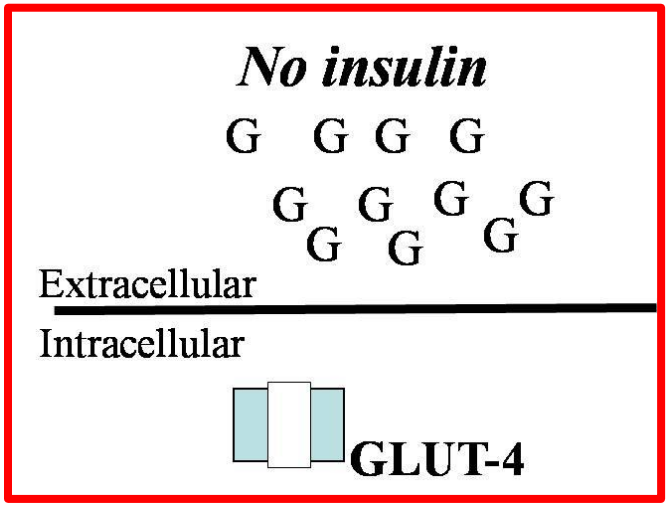


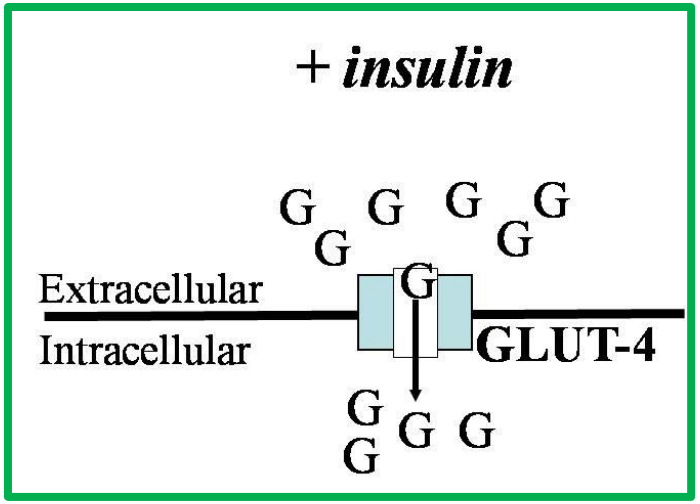
# Effects of insulin

- acts to lower blood glucose levels

- liver, CNS, red blood cells and kidney are able to take up glucose unaided
- Skeletal and cardiac muscle and adipose tissue require insulin for glucose uptake

•Insulin triggers the insertion of GLUT4 glucose transporters into the plasma membrane enabling facilitated diffusion of glucose into fat and muscle cells




- also decreases glucose production in liver, stimulates glycogen synthesis in liver and muscle, promotes amino acid transport and protein synthesis, and inhibits glucagon secretion

# Glucagon

Glucagon is a catabolic hormone, that is, it mobilizes glucose, fatty acids and amino acids from stores into the blood.

Single chain polypeptide

Secreted by $\alpha$ cells in response to a fall in blood glucose levels

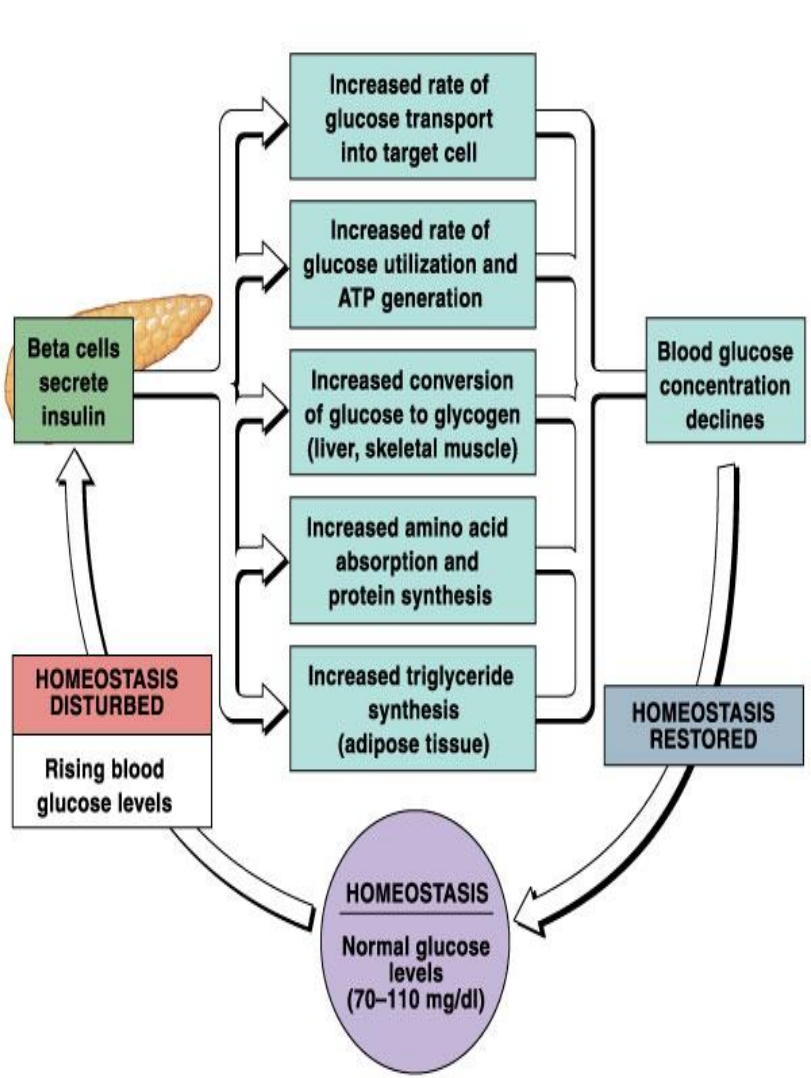
The primary effect of glucagon is to raise blood glucose levels by:

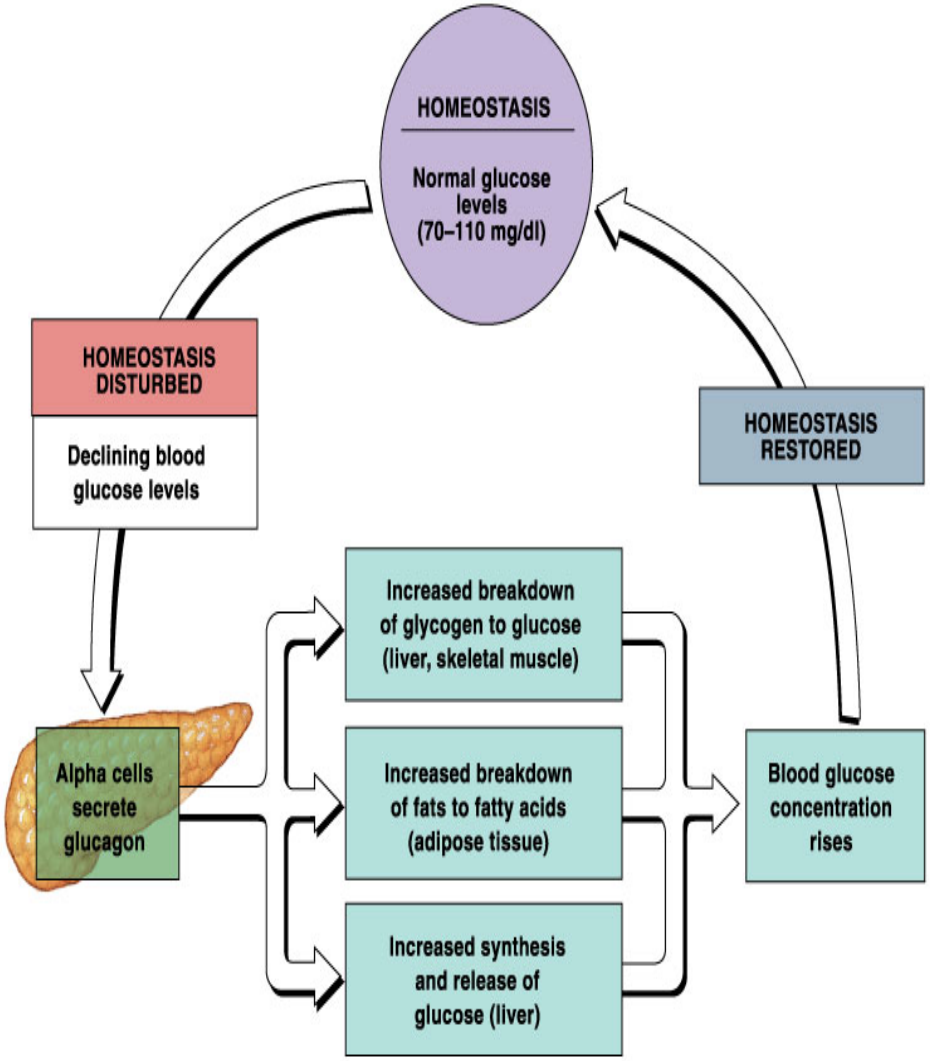
1. Stimulating gluconeogenesis (formation of glucose from lactate)
2. Mobilising liver glycogen (glycogenolysis releases glucose from the liver)

Other effects:

1. Increases lipolysis (breakdown of fats in adipose tissue)
2. Stimulates insulin release (so allowing newly-formed glucose entry into the cells)

# Hormonal regulation of blood glucose levels



# Endocrine disorders - pancreas

## Diabetes Mellitus

**Symptoms**: polydipsia (increased thirst), polyuria (increased frequency and volume of urination), sweet tasting urine (hence *mellitus*).

**Reason**: Excessive blood glucose due to lack of insulin function. Normally glucose is reabsorbed by the kidney. If the glucose concentration exceeds that which can be reabsorbed (~11mmol/L), glucose is lost in the urine (*sweet urine*). Glucose takes water with it due to osmosis (*polyuria*). This induces dehydration (*polydipsia*).

**Pathophysiology**:

- Type 1 (juvenile onset) - insufficient production of insulin, often due to autoimmune destruction of pancreatic β cells
- Type 2 (adult onset) - characterised by insulin resistance – insulin is secreted normally, but neither stimulates glucose storage as glycogen by the liver nor activates glucose uptake into fat and muscle cells.
- In both, cells respond as if glucose levels are low, utilising proteins and lipids as alternative energy sources. Leads to protein depletion, wasting, ketosis, and acidosis. **If you have Type 2 diabetes in your family, you can prevent/delay onset by eating right and exercising**

# Endocrine disorders - pancreas

## Hyperinsulinaemia

**Symptoms**: low blood glucose concentrations in neonates

**Reason**: Excessive insulin secretion reduces blood glucose to dangerously low levels. Consequent decrease in blood glucose levels causes brain damage if glucose is not maintained therapeutically.

**Pathophysiology**:

- ***Genetic defects*** in ATP-sensitive potassium channels in β cells results in dysregulation of insulin secretion by glucose.
- ***Environment in utero*** – uncontrolled blood sugar in diabetic mother can lead to compensatory hyperplasia foetal pancreatic beta cells
- ***Insulinomas –*** pancreatic beta cell tumour secreting high insulin

**Hyperinsulinaemia is often associated with type 2 diabetes, obesity and metabolic syndrome** - the cells of the body become resistant to the effects of insulin as the receptors which bind to the hormone become less sensitive to insulin concentrations resulting disturbances in insulin release and high circulating levels

# Insulin production for treatment

1916 - Romanian Professor, Nicolae Paulescu, develops pancreatic extract that lowers blood sugar in diabetic dogs. WW I prevents studies continuing. Publishes in 1921.

1921 - Frederick Banting and Charles Best successfully **purified insulin** from a dog's pancreas
Banting (& John JR MacLeod) awarded Nobel Prize 1923

1936 - insulin with added fish sperm protamine - slower release, as body breaks down slowly

1955 - Frederick Sanger characterised amino-acid sequence of human insulin. Nobel Prize 1958

1960s - Dorothy Crowfoot-Hodgkin revealed the physical structure of insulin. Nobel Prize 1964

1970s - attempts to produce insulin that mimicked better how the body's natural insulin worked; releasing a small amount all day, with surges occurring at mealtimes. Spliced a **rat insulin gene** into a bacterium that then produced insulin 1977

1980s - biotechnology revolution: Eli Lilly Corp. produced a **human insulin** … first approved **genetically engineered pharmaceutical,** contained no animal 'contaminants'.

1990s - **Analog insulin**; change of a.a. sequence - clumps less and dispersed more readily into the blood - starts working in the body minutes after an injection.

By 2001 - 95% of insulin users in most parts of the world take some form of human insulin. All companies focus on synthesizing human insulin or insulin analogs

2005-2006 - approval of buccal/oral insulin (Oralin) and first inhaled insulin (Exubera)

2010-2020 – Smart pen (InPen), 3 day disposable patches (Humalog), Insulin pumps and pod (Bluetooth/iphone technologies)

***The Nobel Prize in Physiology or Medicine 1923***

***The Nobel Prize in Chemistry 1958***

***The Nobel Prize in Chemistry 1964***