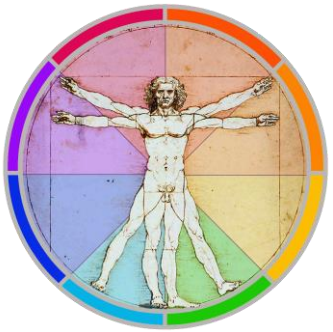
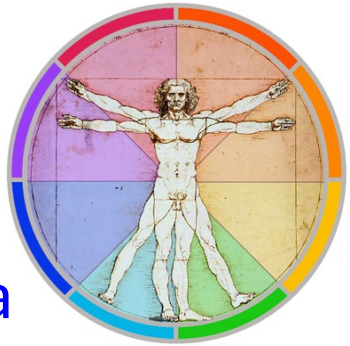
HUBS191 Lecture Material

This pre-lecture material is to help you prepare for the lecture and to assist your note-taking within the lecture,
it is NOT a substitute for the lecture !



Please note that although every effort is made to ensure this pre-lecture material corresponds to the live-lecture there may be differences / additions.

HUBS 191 2025
Lecture 29



Endocrine V: Homeostasis of plasma glucose and Diabetes Mellitus

- Plasma Glucose Homeostasis
- Pancreatic hormones, insulin and glucagon
- Fed vs Fasting metabolic states
- Diabetes Melletis

Philip Kelly
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Lecture Objectives (Updated)

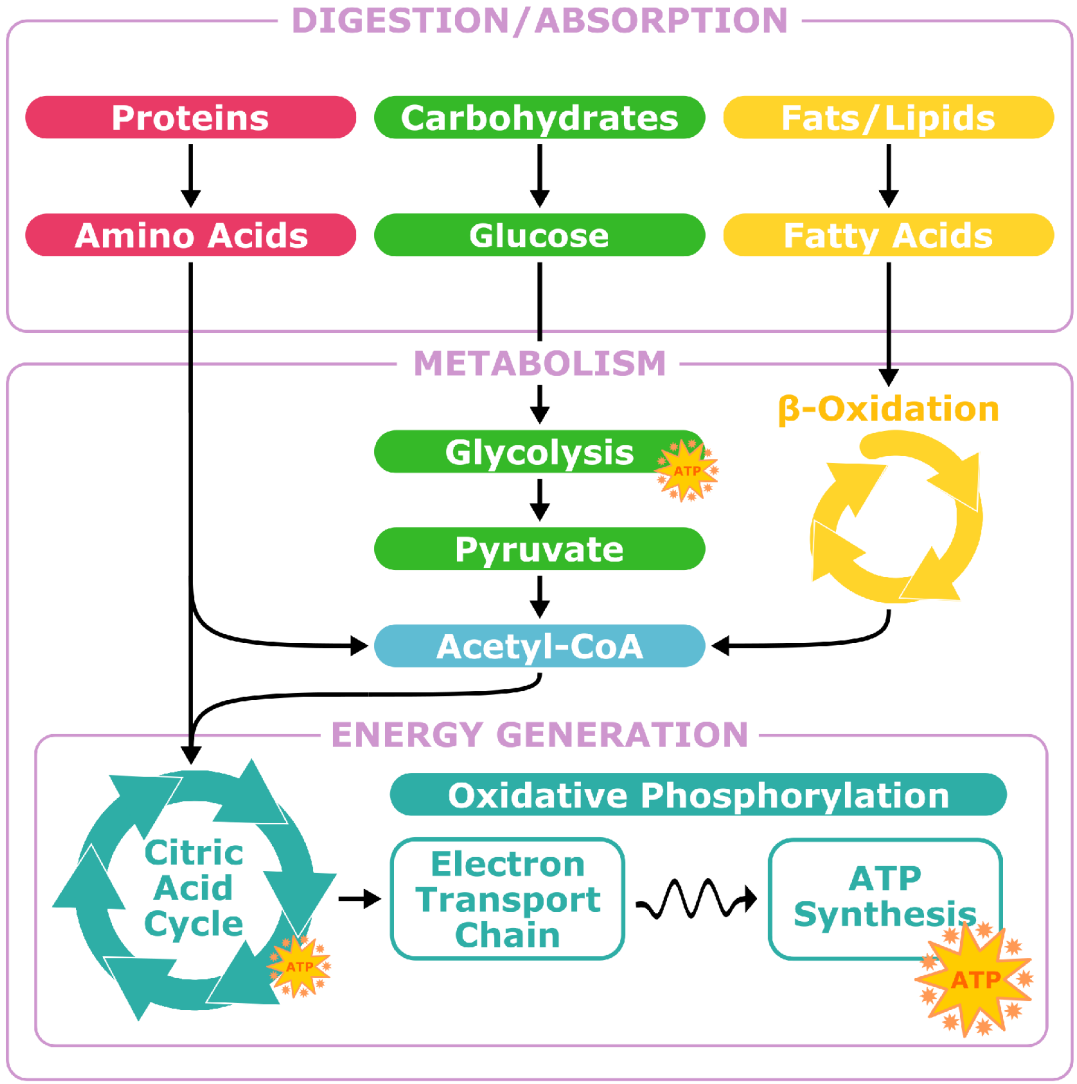
- Outline the importance of plasma glucose homeostasis
- Be able to state typical reference range for fasting and non-fasting glucose concentration.
- Describe the location and structure of the pancreas and name the hormones produced by the alpha and beta cells.
- Understand the effects of insulin and glucagon on muscle, adipose and the liver.
- Outline the difference between the fed and fasting metabolic states.
- Understand how insulin and glucagon work together to maintain blood glucose homeostasis.
- Outline the causes of diabetes mellitus and the potential consequences if not adequately treated
- Briefly outline how diabetes may be treated and managed

- **Normal reference range for plasma glucose concentration**
  - 3.5 to 6 mmol/L (fasting)
  - 3.5 to 8 mmol/L(non-fasting)

  Note: Textbook uses different units ie 70-110 mg/dL

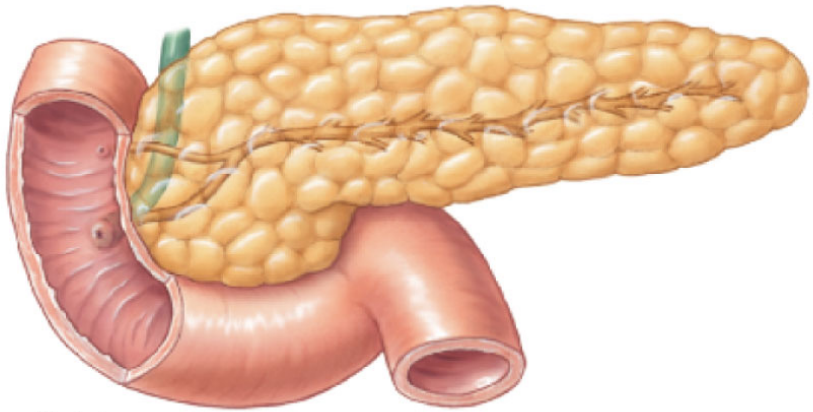
- **Why is blood glucose concentration so important?**
  - brain cells are largely dependent on glucose as energy source
  - other cells are better able to use alternative substrates for ATP production when glucose levels are low.

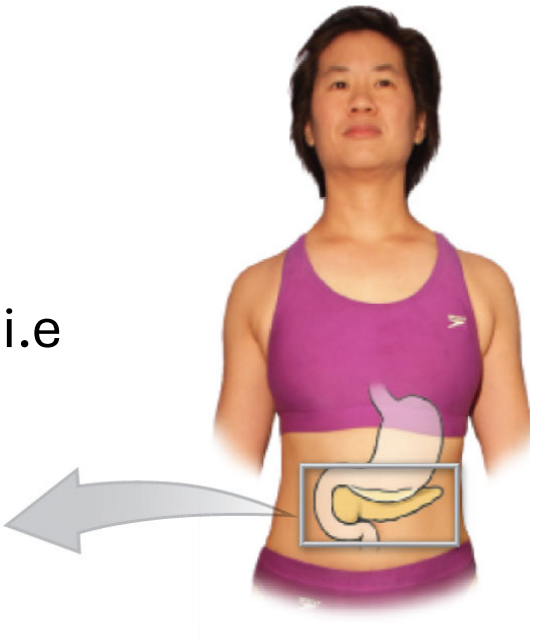
- **Prolonged <u>HIGH</u> blood glucose causes its own problems in various organs**



- The **PANCREAS** is located in curve of duodenum and consists of head, body and tail

- 99% of pancreatic cells are clustered into acini that secrete enzymes into ducts which empty into intestine i.e **exocrine** glands





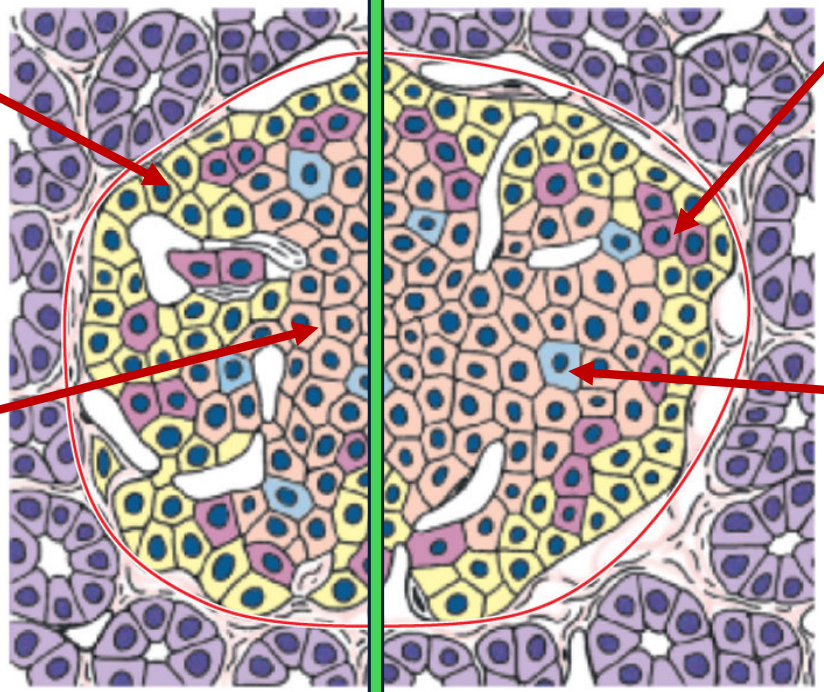
- Small clusters of **endocrine** cells scattered amongst acini = pancreatic islets or Islets of Langerhan's.
  - There are normally 1-2 million islets in the human pancreas……

Alpha cells

- Secrete glucagon
- Increases BGL

Beta cells

- Secrete insulin
- Reduces BGL

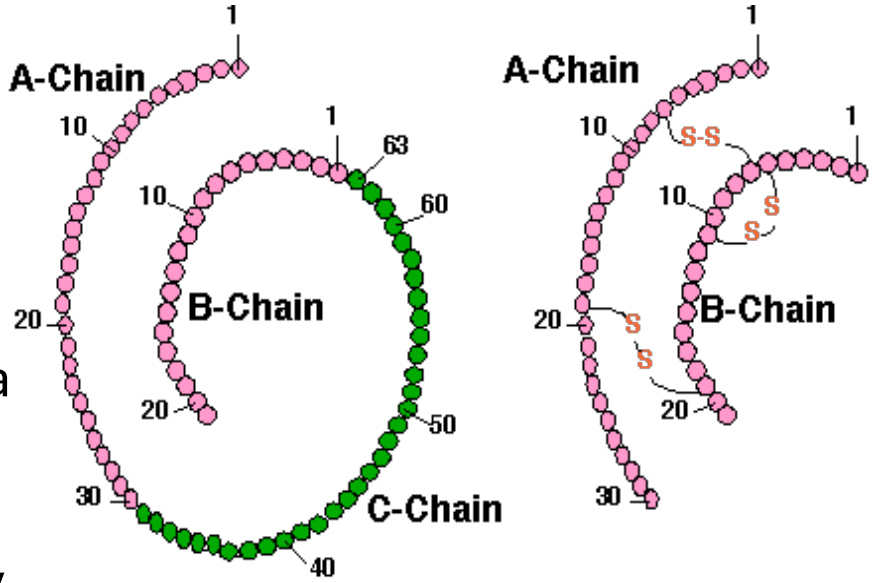


Delta cells

Pancreatic Polypeptide (PP cells)

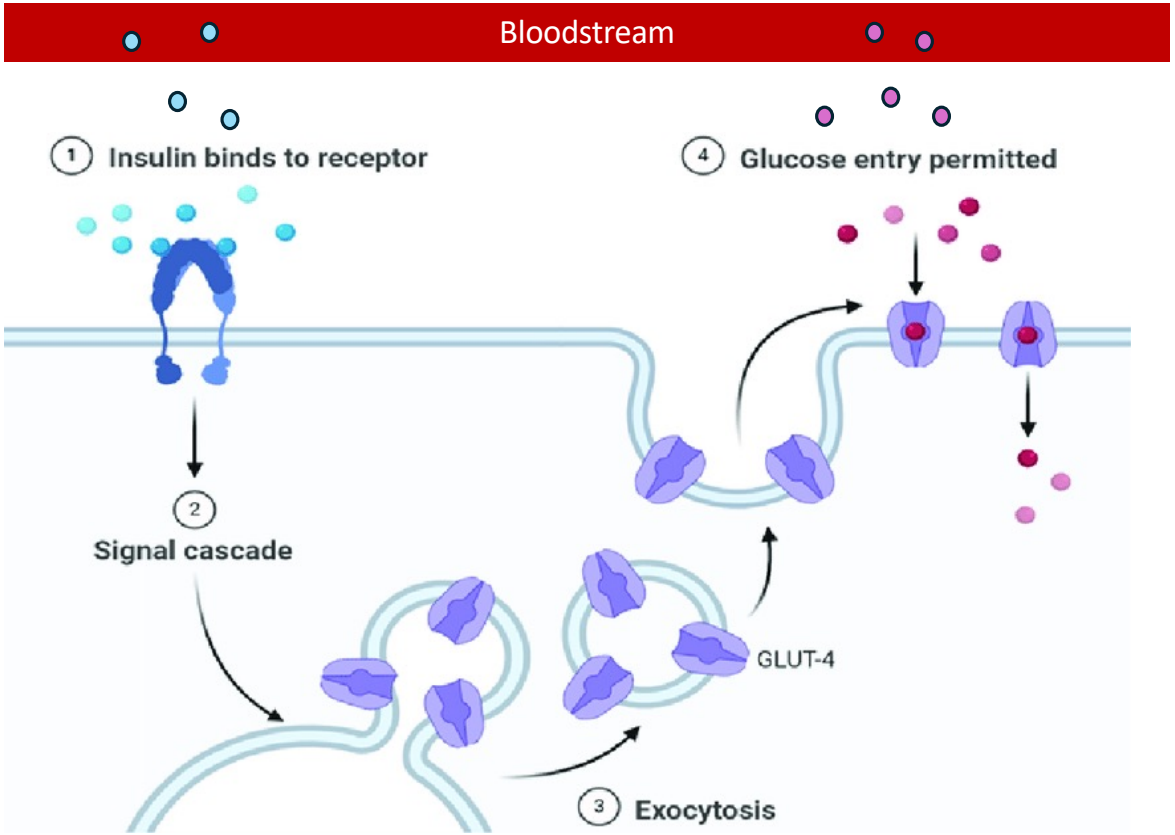
Insulin

- Protein hormone Initially synthesized on RER of beta cells as preprohormone with A, B and C chains
- C chain removed in Golgi apparatus and packaged into secretory vesicles
- Insulin (and C peptide) released from beta cells when BGLs rise
- Circulates unbound in plasma and mostly cleared from circulation within 10-15 minutes



Insulin corrects **hyperglycemia** by facilitating glucose uptake into cells of most body tissues

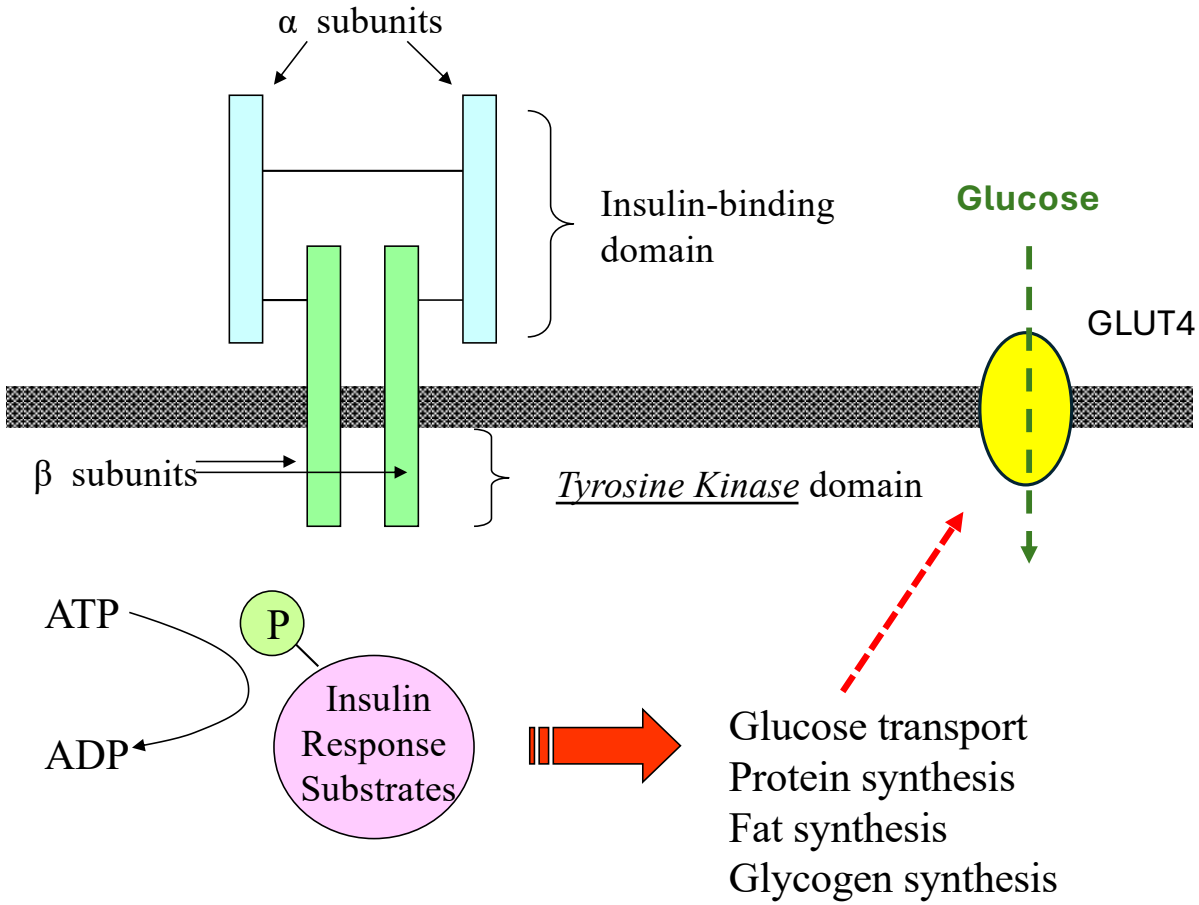
Without insulin, glucose can't be utilized by most cells for energy AND blood glucose levels will be too high



Reference: Chaurasiya, A., Singh, R., & Shah, A. (2020).Interaction between oxidative stress and diabetes: a mini-review. Journal of Diabetes & Metabolic Disorders, 7(2), p59 Fig1. Activation of the glucose transporter GLUT4 by insulin.

- Insulin binds to alpha subunits
- beta subunits then get phosphate groups attached from ATP
- Beta subunits then able to phosphorylate proteins inside the cell that mediate insulins effects
  - Insulin response substrates
- Insertion of GLUT4 transporters into cell membrane of muscle and fat cells
- Activation/inactivation of specific enzymes pathways in various cells
- The exact effect will depend on the type of cell

Insulin Receptors (member of Receptor Tyrosine Kinases)

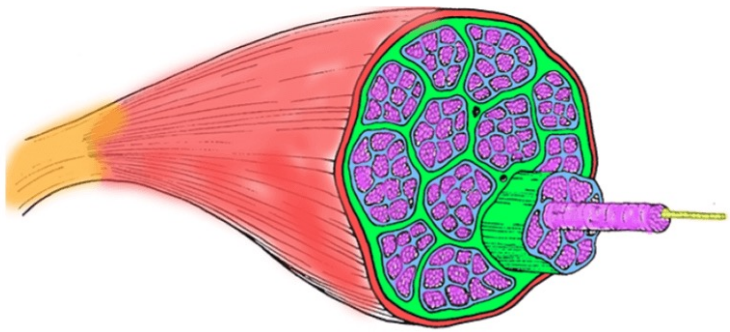


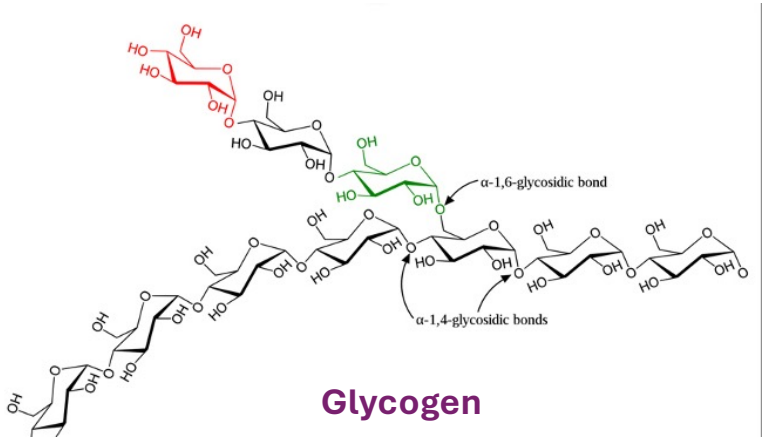
Effects of Insulin on **Skeletal Muscle**

- Increased glucose entry into muscle cells via GLUT4 (insulin dependent)
- Increased glycogen synthesis in muscles
  - (assuming not exercising at the same time)
- Increased transport of amino acids into muscle (and other cells)
- Increased protein synthesis
- Inhibition of protein breakdown

Note: When glucose and insulin levels low, muscle uses fatty acids for energy

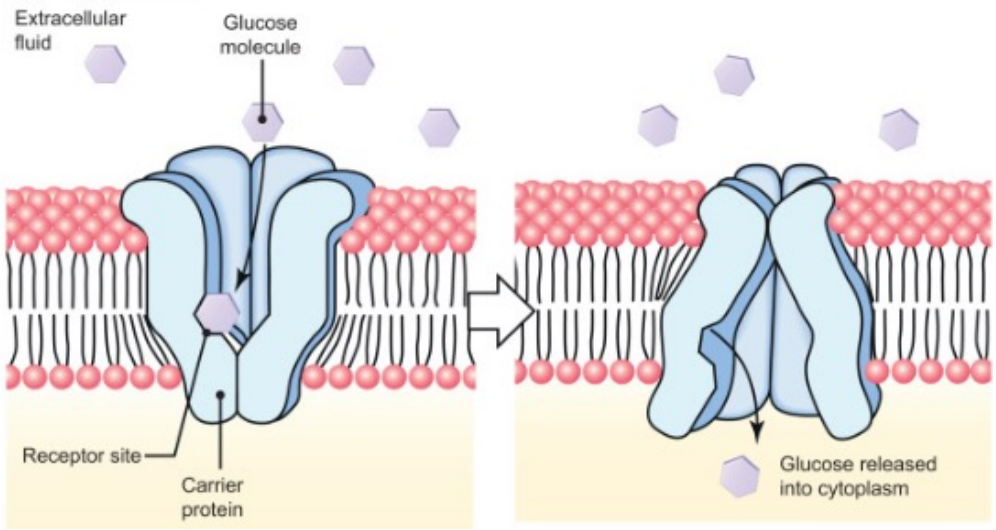
- Exercise itself causes translocation of GLUT4 to cell membrane in skeletal muscle





Effects of Insulin on Adipose (fat tissue)

- Increased glucose transport into adipose cells via GLUT4 (facilitated diffusion)
- Increased synthesis and storage of triacylglycerides
- Insulin inhibits lipolysis (TAGs to fatty acids)

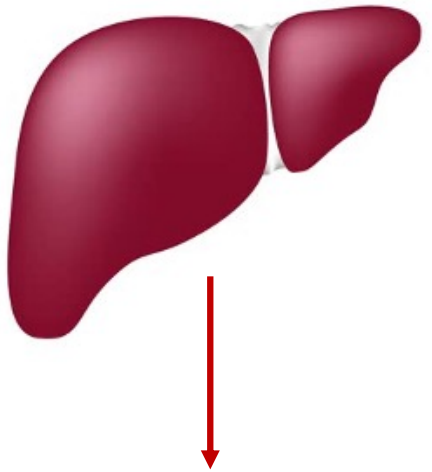


Specific molecule such as glucose binds to receptor site on the integral membrane protein transporter

Shape of the protein then changes, moving the molecule across the plasma membrane.

https://www.sciencedirect.com/topics/neuroscience/facilitated-transport

Effects of Insulin on **Liver**

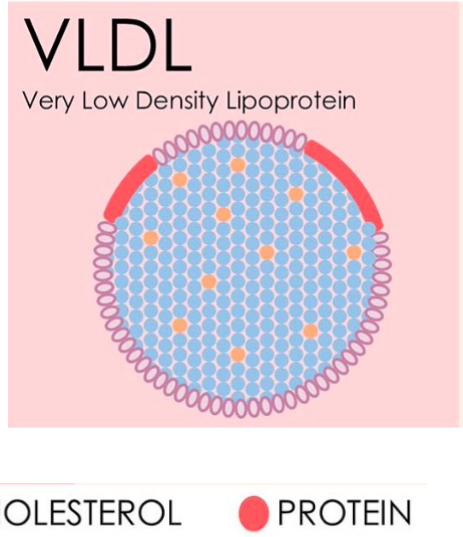


1. uptake of glucose and conversion to glycogen.

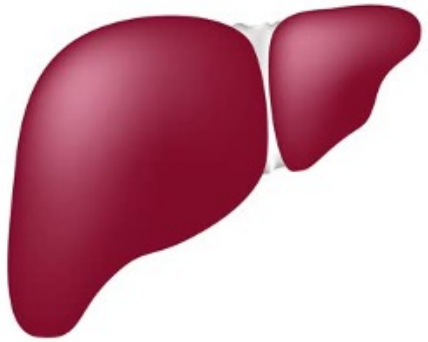
- Entry of glucose into hepatocytes is mainly via GLUT2
  - (insulin independent)

2. Fatty acid synthesis

- When the quantity of glucose entering liver cells is more than can be stored as glycogen (or used for hepatocyte metabolism) then insulin promotes conversion of excess glucose into **fatty acids.**
- Fatty acids packaged into VLDL as triglyceride
- VLDL enters blood and transports triglycerides to other tissues



Effects of Insulin on **Liver…**



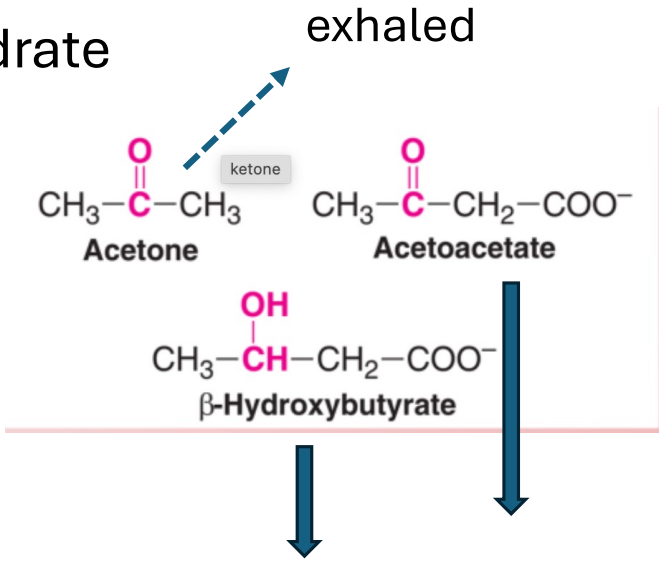
3. Inhibits glycogenolysis

- (breakdown of glycogen to glucose)

4. Inhibits gluconeogenesis

- (production of ‘new’ glucose from non-carbohydrate sources e.g. amino acids, glycerol, lactate)

5. Suppresses the formation of ketone bodies (acetoacetic acid, beta-hydroxybutyric acid and acetone)



Utilized by other cells for ATP production

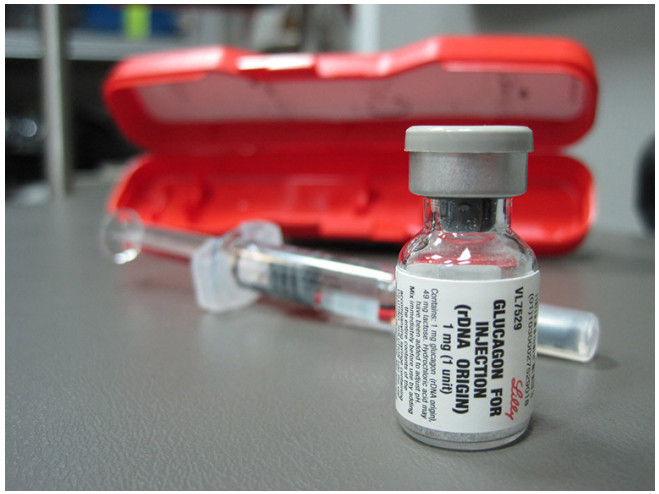
- Insulin can be thought of as **“signalling that the body has been fed”**
  - Promotes uptake and storage of nutrients
    - Glucose → glycogen (muscle and liver)
    - Glucose → fatty acids and triclycerides (adipose and liver)
    - amino acids → protein (muscle and various other cells)

- Conversely, **if there is no insulin then the body behaves as if it is “starved”**
  - Mobilizing glycogen stores in muscle and liver
  - Breaking down protein to its constituent amino acids which can be used for energy or to make new glucose in the liver (gluconeogenesis)
  - Mobilizing fat stores to increase lipids levels in blood
  - Increasing ketone production which can be used by various tissues (including brain) as an energy source – ‘glucose sparing’

Glucagon

- Polypeptide hormone secreted by alpha cells of pancreatic islets primarily in response to **HYPOGLYCEMIA** (low blood glucose)
  - Exercise can also stimulate glucagon secretion

- Glucagon exerts its effects (primarily on the **liver**) via activation of receptors that utilize cAMP as second messenger.



- **Results in activation of enzymes which:**
  1. Cause breakdown of glycogen to glucose (glycogenolysis)
  2. Promote production of “new glucose” by hepatocytes (gluconeogenesis)
  3. Promote release of glucose from liver cells into blood
  4. Promote breakdown of triglycerides and release of fatty acids from adipose

Blood Glucose Homeostasis Summary

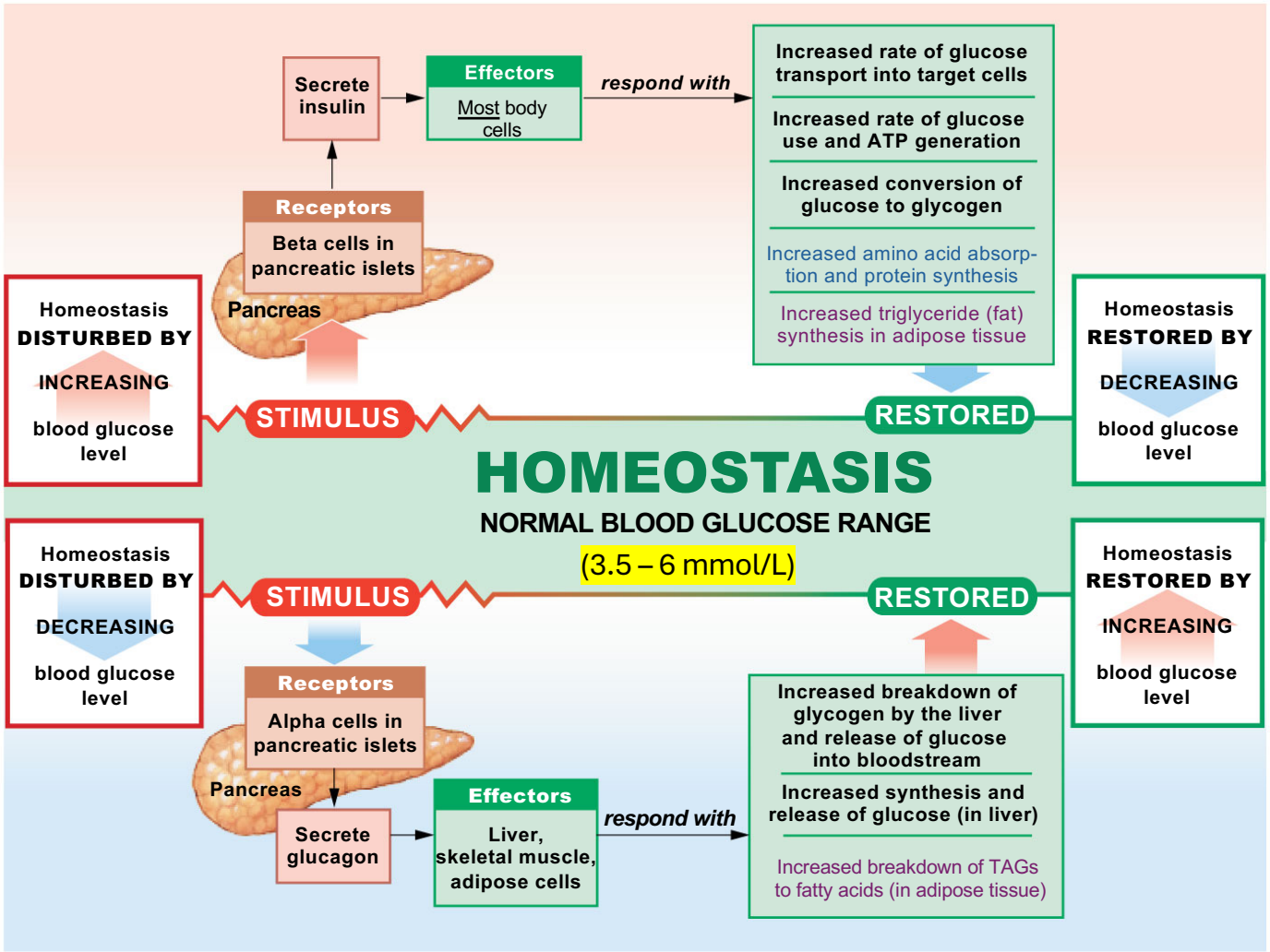


Figure 16.11 3

Diabetes Mellitus

- ***'Diabetes'*** derived from Greek – 'siphon' or 'pass through'
- ***'Mellitus'*** derived from Latin for 'honey' or 'sweet'

- Historically referred to a disease state characterized by:
  - **Polyuria** (passing large volumes of urine)
  - **Polydipsia** (excessive drinking / thirst)
  - **Polyphagia** (excessive hunger)

"...a chronic affliction characterized by intense thirst and voluminous, honey-sweet urine; the melting of the flesh into urine."

(Aretaeus of Cappadocia, first century AD)

Type I Diabetes Mellitus - Essentially NO insulin production by beta cells

Autoimmune destruction of pancreatic beta cells, thought to be due to some environmental trigger (e.g. viral infection) combined with genetic predisposition

Acute Symptoms Type I DM

- Passing urine frequently (polyuria)
- Very thirsty and drinking lots (polydipsia)
- Excessive hunger (polyphagia)
- Tiredness
- Weight loss
- Decreased concentration
- Mood changes
- Tummy Pain

Chronic

- Poor healing
- Increased infection risk
- Cardiovascular Disease
- Renal Disease
- Diabetic retinopathy
- Diabetic neuropathy

Treatment of Type 1 Diabetes is INSULIN!

(other dietary and exercise management strategies may be involved but NEED INSULIN)

Treatment with insulin causes risk of HYPOGLYCEMIA

(Symptoms vary among individuals but tend to be consistent for each person)

1. Symptoms related to activation of the SNS
    - Tachycardia
    - Palpatations
    - Diaphoresis
    - Tremor
    - Pallor
    - Anxiety

2. Due to inadequate blood glucose for normal brain function:
    - Headache
    - Dizziness
    - Irritability
    - Fatigue
    - Confusion
    - visual changes
    - hunger….

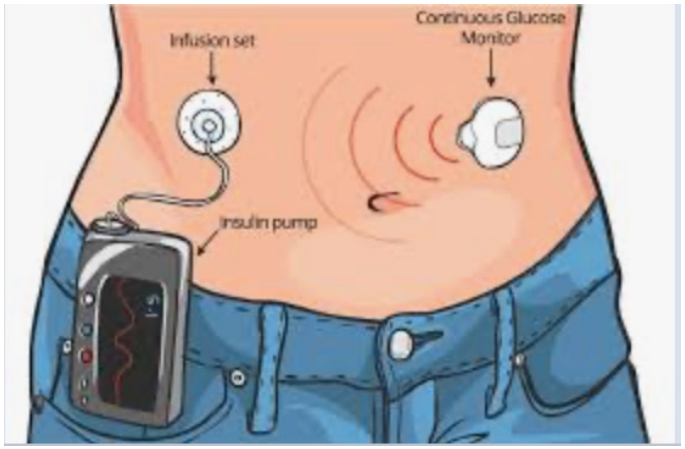
Continuous Glucose Monitors (CGMs)

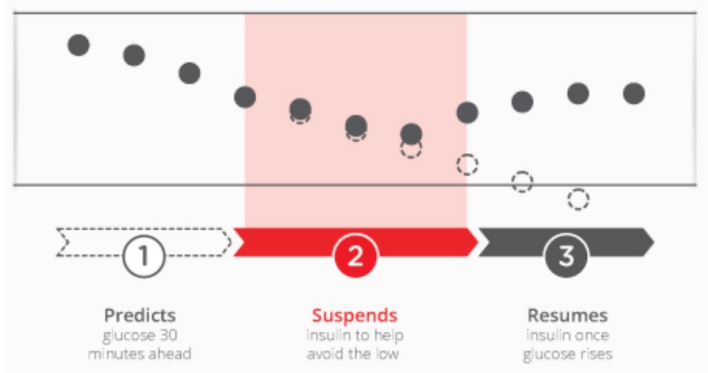
- Subcutaneous BGL sensor transmits to device
- Person adjusts s/c insulin dose accordingly

https://www.diabetes.org.nz/blog/cgms-and-winz

CGM coupled to insulin pump

- Subcutaneous BGL sensor transmits to device
- Pump algorithm adjusts infusion rate accordingly
- Can utilise feedforward AND negative feedback

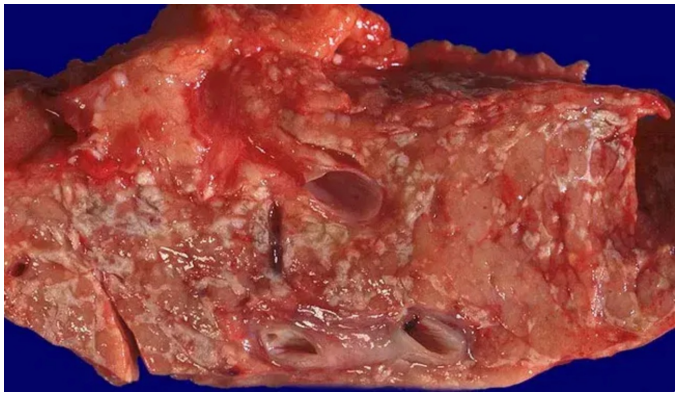




Type II Diabetes Mellitus

- Reduced sensitivity to the effects of insulin (hyposensitivity)
- **Common causes** : Inactivity, poor diet, obesity
- Insulin secretion may be high in early stages (to control high BGL)
- Later in disease, beta cells may get 'worn out' leading to progressively lower insulin secretion and worsening blood glucose control (hyposecretion)

Some other conditions that can cause raised blood glucose include:



- Diseases that damage pancreas
  - Pancreatitis, cystic fibrosis
- Some medications (e.g glucocorticoids)

https://www.webpathology.com/images/gastrointestinal/pancreas/acute-and-chronic-pancreatitis/43513

Treatment of Type II Diabetes

1. Aim to **reduce weight** by 10-15% in early disease to achieve remission

2.**Metformin**

- improves insulin sensitivity of cells and reduces hepatic gluconeogenesis

3. Drugs that cause glucose to be lost in urine (**SGLT2 inhibitors**)

4. Drugs that increase insulin secretion

   - **GLP-1 receptor agonists**
   - Sulphonylurea drugs

5. **Acarbose** - slows down absorption of glucose from intestines

Some comparisons between Type 1 and Type II diabetes

- Type 1 always requires insulin
- In type II there is usually enough insulin secretion to prevent ketosis and weight loss but not hyperglycemia
- Both Types I and II can have symptoms of polydipsia and polyuria
- Type II may be treated with diet, exercise and oral medications
- Type II may also end up requiring insulin to maintain BGL control
- Both can result in pathology related to chronic hyperglycemia..

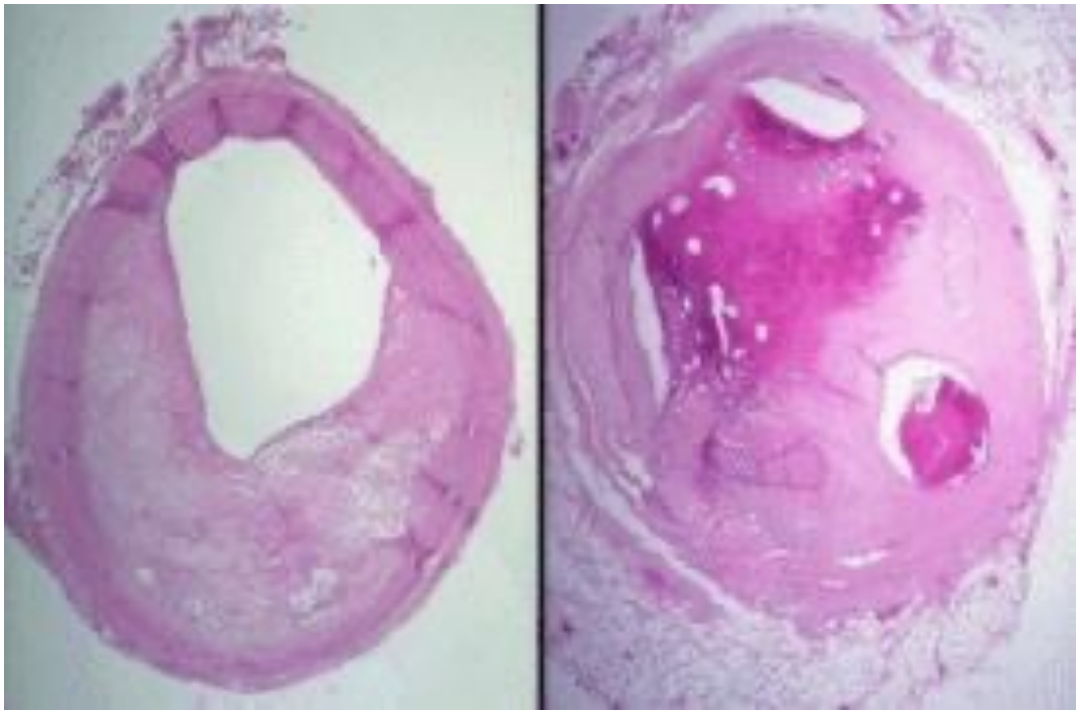
Gestational diabetes may occur in women during pregnancy so important to srceen for this.

Pathological effects of chronic hyperglycemia

Diabetic Retinopathy

Diabetic Nephropathy

Atherosclerosis (CAD, PVD, stroke)



Diabetic Neuropathy, poor wound healing, infection risk.

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