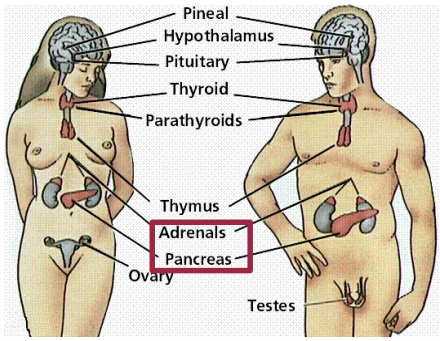
Glucose Homeostasis



Prof Suzanne L Dickson

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Topics

- Glucose homeostasis – the physiological challenge
- Glucostatic hormones that decrease blood glucose.
  - Insulin
  - Incretins
- Glucostatic hormones that increase blood glucose
  - Glucagon
  - Adrenaline
  - Cortisol
  - Growth hormone
- Other hormones
- The clinical context: diabetes mellitus

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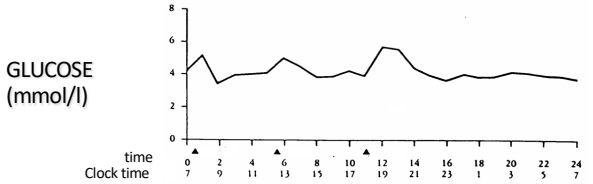
Blood glucose concentration is under tight homeostatic control



Normal range is
4 to 6.5 mmol/L
Learn values!!

Why is it important to control blood glucose?

HIGH BLOOD GLUCOSE IS BAD

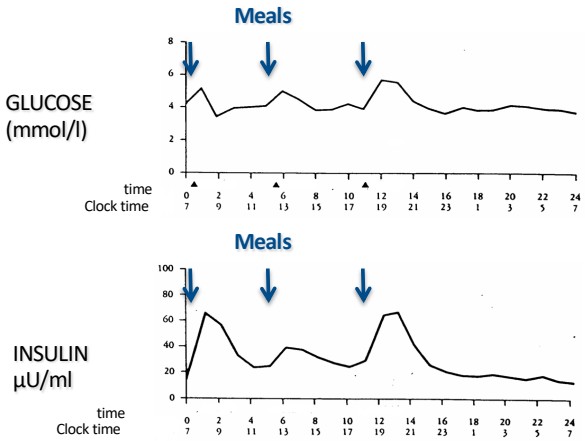
- **CHRONIC.** Persistent high glucose levels leads to many complications as seen in patients with diabetes mellitus (eg fatigue, thirst, retinopathy, kidney failure, diabetic foot etc - see later slides).
- **ACUTE** high levels can be life threatening due to diuresis (fluid loss).

LOW BLOOD GLUCOSE IS BAD

–An insufficient glucose supply to the brain will cause coma and death.

Glucose homeostasis – the problem of meals

The physiological challenge: to maintain <6.5 mmol/l no matter what and how much we eat.



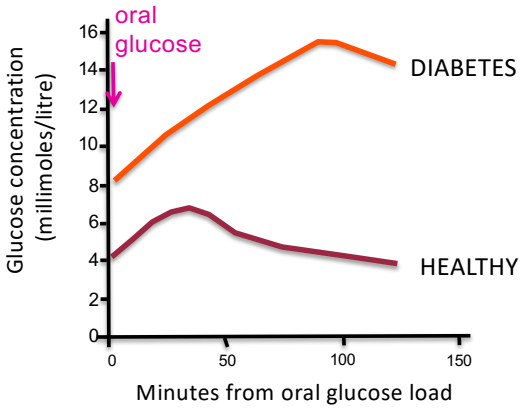
The most important hormone that reduces blood glucose after meals is **INSULIN**. Blood insulin levels are determined by both the amount of food we eat and its composition.

INSULIN REDUCES BLOOD GLUCOSE BY MOVING IT INTO CELLS, WHERE IT CAN BE USED AND/OR STORED.

Oral glucose tolerance test: a diagnostic tool for diabetes

How well does the body tolerate an acute glucose challenge?

- Overnight fast
- Oral glucose drink
- Measure glucose
  - ✧ Fasting level
  - ✧ How large an increase?
  - ✧ How rapid recovery?
- More sensitive than fasting glucose to identify (pre-)diabetes.

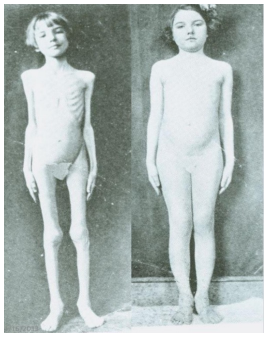


In healthy individuals blood glucose concentrations are tightly regulated. Fasting normal range: **4-6 mmol/l**

Diabetes mellitus

TYPE 1

- Blood glucose levels high
- No/very low blood insulin levels

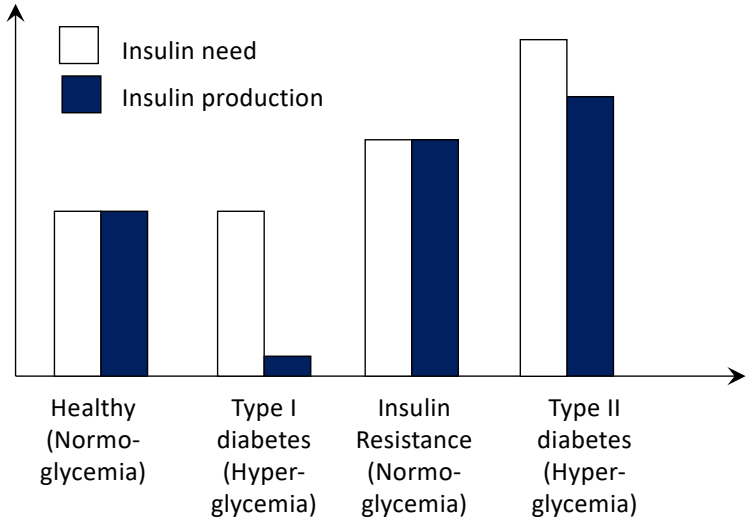


This girl would have died within days without insulin treatment.

TYPE 2

- Blood glucose high
- High insulin levels (but insufficient for need)
- **Insulin resistance** - tissues cannot take up glucose.
- Commonly associated with obesity

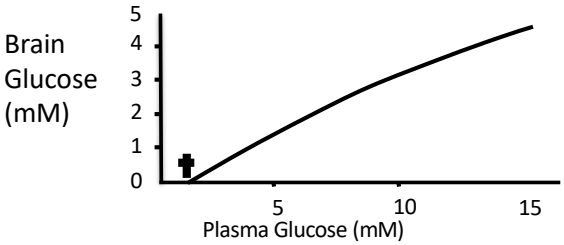
Insulin need and insulin production become uncoupled in disease



Glucose homeostasis – the problem of fasting

The physiological challenge is to ensure plasma glucose remains high enough to supply enough glucose to the brain when fasting and between meals.

- Normally the brain only uses **glucose** as its energy source.
- After several days fasting, the brain can use **ketones** (eg acetyl acetate or ß-hydroxybutyrate) as an alternative fuel. BUT, at best, ketones only provide 50% of the brain's energy, the rest must come from glucose.



Death occurs when plasma glucose levels fall below 1 mM

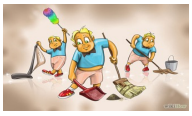
Glucose homeostasis – the problem of fasting

How can we maintain >4 mmol/l if we don't eat?

- GET GLUCOSE FROM GLYCOGEN STORES IN LIVER (**Glycogenolysis**).
- MAKE MORE GLUCOSE. Liver synthesizes glucose from non-carbohydrate carbon substrates (eg lactate, glycerol) and amino acids. (**Gluconeogenesis).**
- DON'T LET ORGANS USE GLUCOSE (& KEEP FOR BRAIN INSTEAD). Less glucose uptake by muscle & fat (**insulin resistance** i.e. unable to respond to insulin).

Go to the bank

Make more money



Stop spending

I don't have any money

The main glucose-regulating hormones

- **INSULIN**
- **"INCRETINS" (eg. GLP-1)**
- **GLUCAGON**
- **ADRENALINE**
- **GROWTH HORMONE**
- **GLUCOCORTICOIDS**

Decrease blood glucose after meals

Increase blood glucose between meals

MAIN HORMONES

In addition, the following hormones have beneficial (good) effects on blood glucose:

- **LEPTIN** deficiency during fasting decreases blood glucose – as leptin helps glucose entry to muscle cells.
- **IGF-1** has insulin-like effects to reduce blood glucose.
- **GHRELIN** (released in fasting) increases blood glucose, probably by inducing insulin resistance (could be growth hormone-dependent)

Topics

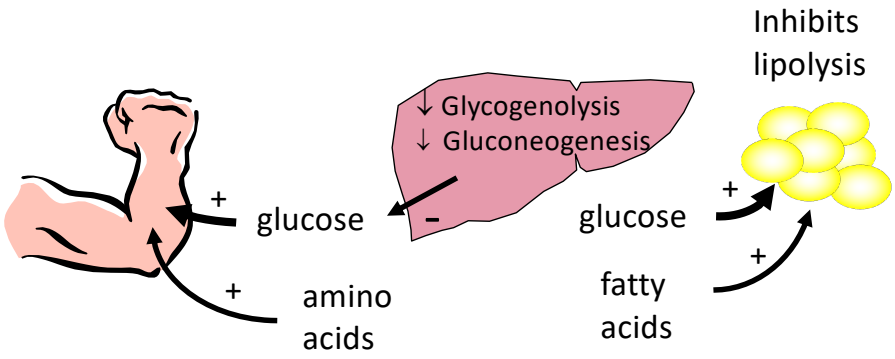
- Glucose homeostasis – the physiological challenge
- **Glucostatic hormones that decrease blood glucose.**
  - **Insulin**
  - **Incretins**
- Glucostatic hormones that increase blood glucose
  - Glucagon
  - Adrenaline
  - Cortisol
  - Growth hormone
- Other hormones

Insulin's functions

- **Primary target tissues:** liver, adipose tissue, and skeletal muscle.
- **Insulin's major function**: to facilitate cellular glucose uptake in many tissues (esp muscle and fat but not brain).
- **Insulin's mechanism** for glucose homeostasis:
  - Increases glucose transport into insulin-sensitive cells
  - Enhances cellular utilization and storage of glucose
  - Enhances utilization of amino acids
  - Promotes fat synthesis

Insulin's functions

Insulin is released in response to feeding



Insulin transports nutrients to organs where they can be used or stored. It also suppresses breakdown of stores.

How does glucose get into cells? Glucose transporters

- Glucose enters cells by ***facilitated diffusion,*** involving glucose transporters
- >14 kinds of glucose transporters in man (GLUT1-GLUT14). GLUT1-4 are best characterized.

	Tissue	Function
GLUT1	Fetal tissues, blood-brain barrier, brain, red blood cells, colon	Basal glucose uptake by most cells (not neurones). Glucose uptake into brain
GLUT2	**β Cells of islets (pancreas),** liver, kidneys, etc	**Glucose-sensing in pancreas.** Bi-directional glucose flux in liver (uptake glucose for glycolysis, and release of glucose during gluconeogenesis). Transport of glucose, galactose and fructose out of intestinal cells
GLUT3	Brain, placenta, kidneys	Basal glucose uptake including nerve cells
GLUT4	**Brown & white fat, skeletal muscle**	**Insulin- (and exercise)-stimulated glucose uptake.**

Note: SGLT2 (sodium glucose cotransporter 2) is involved in glucose reabsorption in the kidney.
IMPORTANT: SGLT2 inhibitors → glucose loss in urine (i.e. new diabetes medication).

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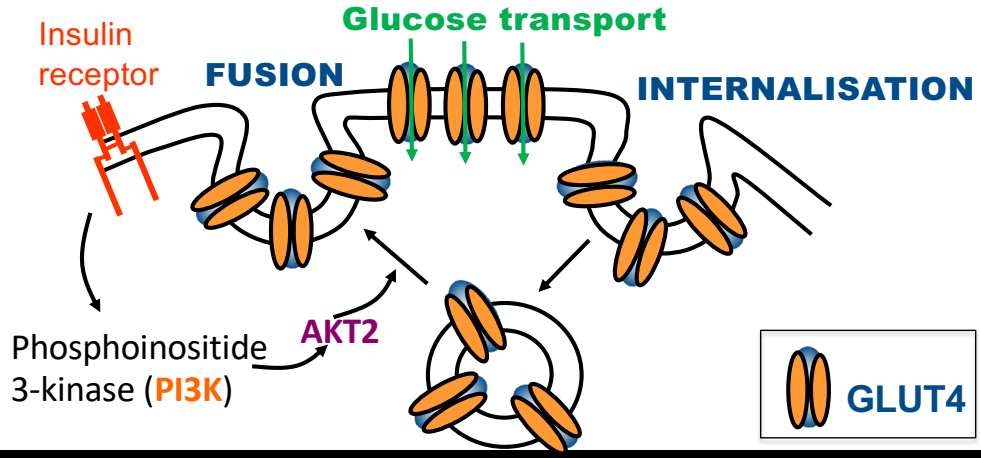
GLUT4 – important for insulin's effects

- Glucose uptake (fat & muscle) - determined by number of GLUT4 transporters on cell surface.
- Insulin action moves GLUT4-containing intracellular vessicles to the cell surface. Exercise also does this (an insulin-independent effect).



GLUT 4 is the only insulin-sensitive glucose transporter

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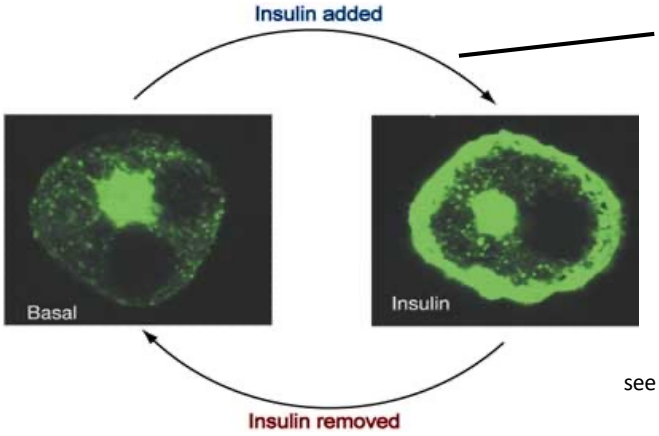
Insulin causes the fusion of GLUT4 containing vessicles with the membrane



Important:
If GLUT4 vesicles do not move to the surface, this can cause type 2 diabetes.
Eg AKT2 mutation

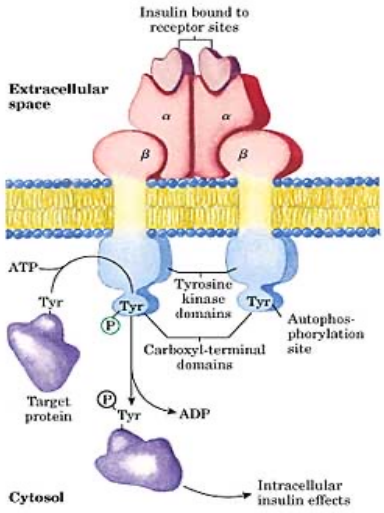
see Saltiel & Kahn (2001) Nature p. 799

Adipocyte transfected with a fusion construct of GLUT4 and enhanced green fluorescent protein

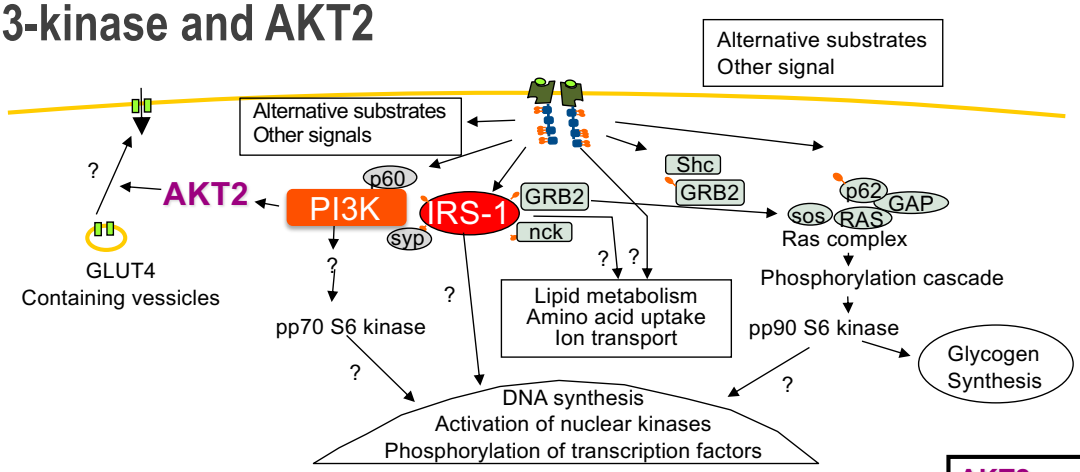
Insulin receptor signalling – some key molecules: IRS-1, PI3-kinase and AKT2

- Plasma membrane receptor
- Locations: mostly fat, liver & muscle
- Belongs to the **tyrosine kinase** (TK) receptor family
- Heterotetramer complex
  - α subunits – binds ligands and β subunits
  - β subunits – anchor receptor in membrane and contain TK activity.
- A key intracellular signal is insulin receptor substrate 1 (**IRS-1**).

NOTE: It is absolutely NOT a G protein coupled rec



Insulin receptor signalling – some key molecules: IRS-1, PI3-kinase and AKT2



Important points

- Insulin receptor activation → **IRS1** phosphorylation (amongst others)
- Phorphorylated **IRS-1** binds to proteins that bear a SH2 homology domain, eg **PI3K.**
- **PI3K** recruits **Akt2** which is required for GLUT4 to translocate to cell membrane.

AKT2 mutation → One identified cause of type 2 diabetes

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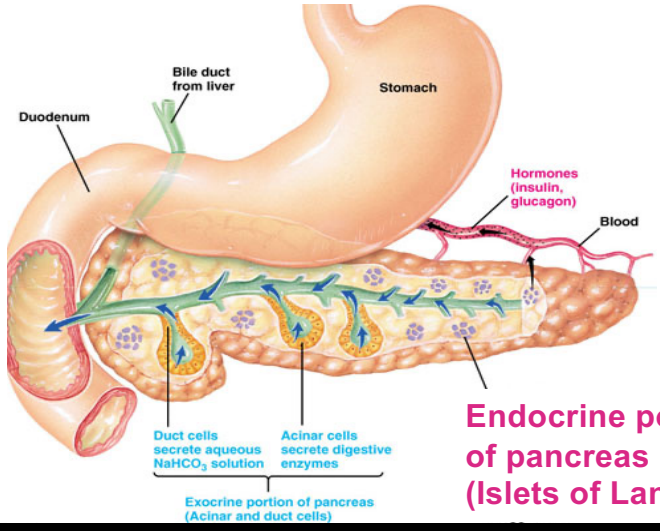
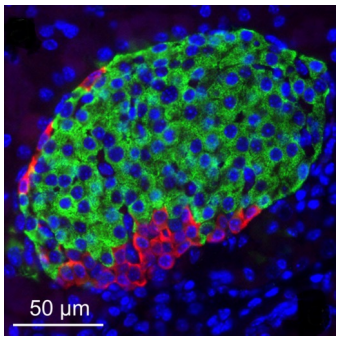
Where is insulin produced?

In the Islets of Langerhans in the pancreas – in the beta cells



Endocrine portion of pancreas (Islets of Langerhans)



Islet of Langerhans. Beta cells (green) produce insulin and alpha cells (red) produce glucagon. The nuclei of the cells is shown in blue. Image of Ge Li/Waterland lab/*Environmental Epigenetics*,2019.

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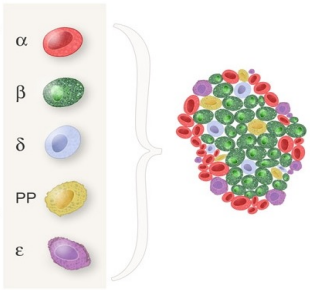
Islets of Langerhans - anatomy



Most abundant cell type is the **beta cell**. These are centrally located.

Alpha cells (20%)
→ **glucagon** (only site produced)
→ ghrelin – (but not major site of production)

Beta cells (~70%)
→ **insulin** (only site produced)
→ amylin (about 1/100 as much as insulin)

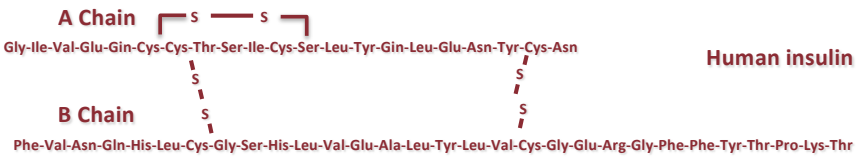
Delta cells (<10%)
→ **somatostatin** (paracrine role?)

PP cells (<5%)
→ pancreatic polypeptide

Epsilon cells (<1%)
→ ghrelin (very little)

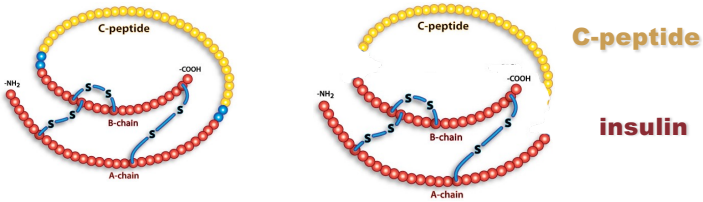
Insulin biosynthesis

- Comprises 2 chains (A and B chains) linked by 2 disulphide bonds.



- Preproinsulin (110 aa), proinsulin (86 aa) & insulin (51 aa).

Folded Pro-insulin

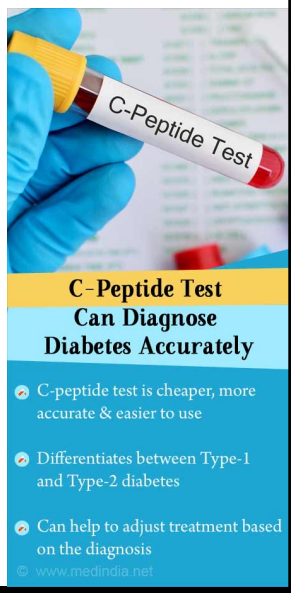


- Insulin, Proinsulin and C-peptide are co-secreted into blood.
- Insulin degredation 40-80% as it passes through liver.

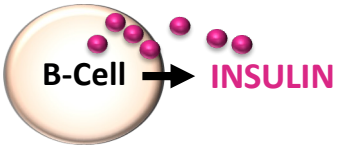
C-peptide is a useful diagnostic tool for beta cell function

- One molecule of C-peptide is produced for every molecule of insulin.
- C peptide does not have a clear biological role.
- **Blood assays for C-peptide enable us to estimate the ability of the pancreas to synthesize insulin.**

DIAGNOSTIC TOOL: Sometimes you want to know about the ability of a patient's pancreas to produce insulin. If a patient is receiving insulin injections, how do you know if what you measure is the insulin injected or insulin produced by the pancreas? ***C-peptide informs on endogenous production but is unaffected by injected insulin.***



Control of insulin secretion



Food substrates:

Glucose is the main controller of insulin secretion.

Amino acids and fatty acids also increase release.

Hormones:

Incretins (eg glucagon-like peptide 1, GLP-1) from enteroendocrine cells in the gut increase release.

Adrenaline (from adrenal glands) decreases release.

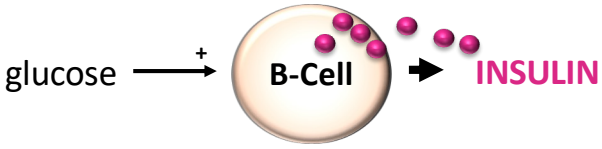
Somatostatin – acts locally in the pancreas (paracrine) to suppress insulin release.

Parasympathetic nervous system:

The sight, smell and taste of food can increase pancreatic insulin release, engaging the vagus nerve.

Control of insulin secretion

1. By blood glucose



- The more glucose is present in the blood, the more will be taken up by the beta cell (involves GLUT2).
- More glucose inside the beta cell causes more **insulin** to be released.

Important Q: How does the pancreas know to adjust **insulin** production according to blood glucose levels (ie according to need)?

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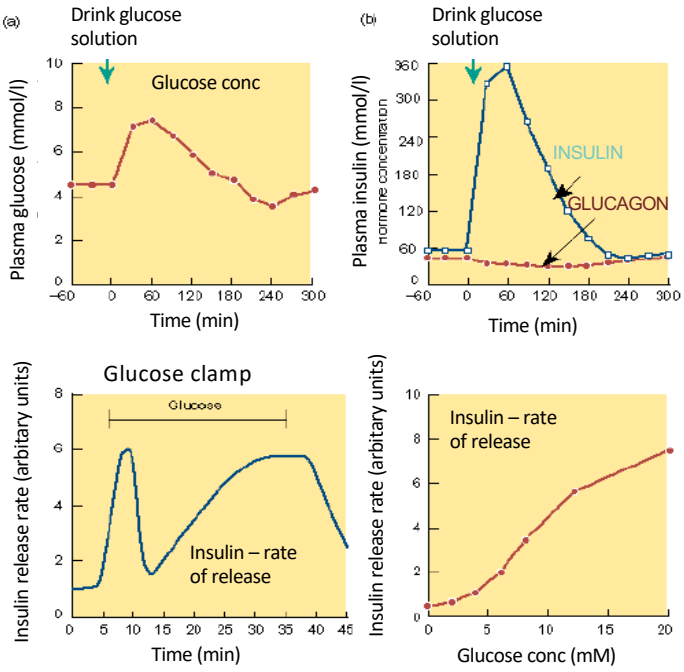

Control of insulin secretion by glucose.

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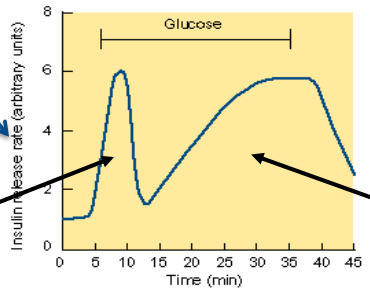
Control of insulin secretion by glucose

Clamp blood glucose at a high level

Note: This is insulin release RATE



Release of stored insulin

Release of newly synthesized insulin

Important Q: How does the pancreas know to adjust insulin production according to blood glucose levels (ie according to need)?

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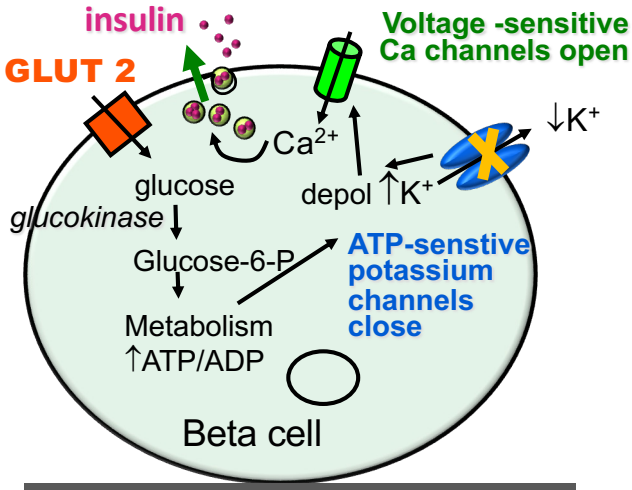
Regulation of insulin secretion from the beta cells by glucose (involves GLUT2)

Glut 2 – large quantity of low affinity glucose transporters.

Blood glucose concentration controls the rate of glucose transport into the beta cell.

Glucokinase (glucose→glucose-6-P). Rate limiting step for for glucose uptake.

↑ **glucose oxidation (glycolysis)**
→ ↑ **ATP/ADP**
→ **K^+ channel closes**
→ ↑ **K^+** → **depolarization**
→ **opening of VSCC**
→ ↑ Ca^{2+} entry
→ ↑ **insulin** release



*Note: **Sulfonylurea** close ATP-sensitive K channels → Treatment for type 2 diabetes*

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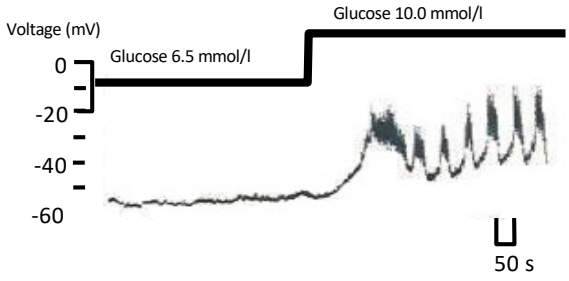
Beta cells respond to an increase in extracellular glucose by depolarizing

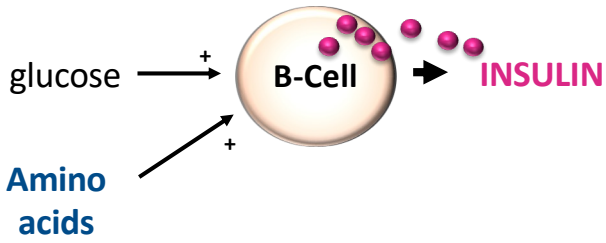


Nature 1968

The membrane potential (V) of a single beta cell within an intact pancreas islet recorded in the presence of 6.5 and 10.0 mM glucose as indicated by the staircase.

Control of insulin secretion

2. By amino acids



Unlike glucose, amino acids do not enter the beta cell by facilitated diffusion. Amino acids have dedicated transporters.

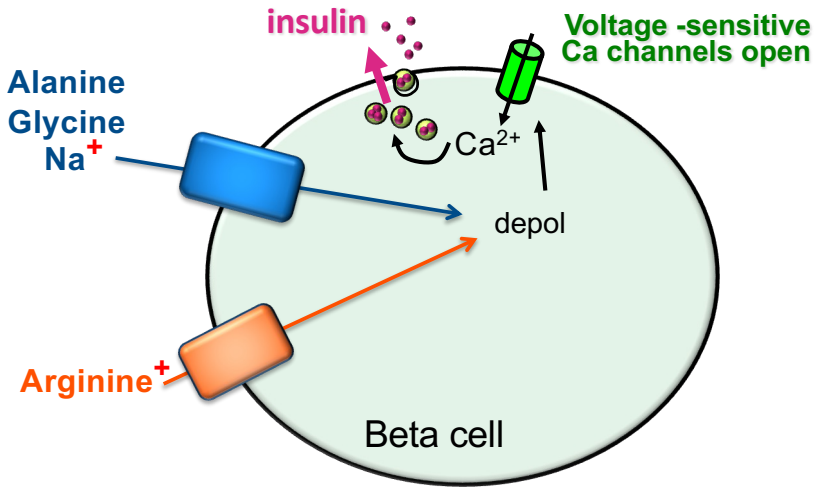
Regulation of insulin secretion by amino acids

Amino acid entry
→ ionic changes
→ depolarization
→ Ca^{2+} uptake
→ exocytosis.

Involves transporters

(i) symporter for Ala, Gly & Na^+.

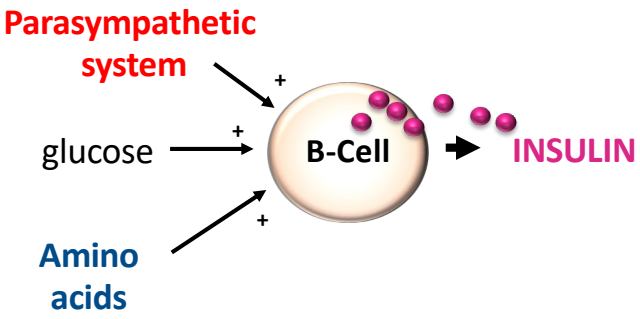
(ii) arginine transport protein



Na^+ entry depolarizes cell.
Arginine$^+$ also depolarizes cell.

Control of insulin secretion

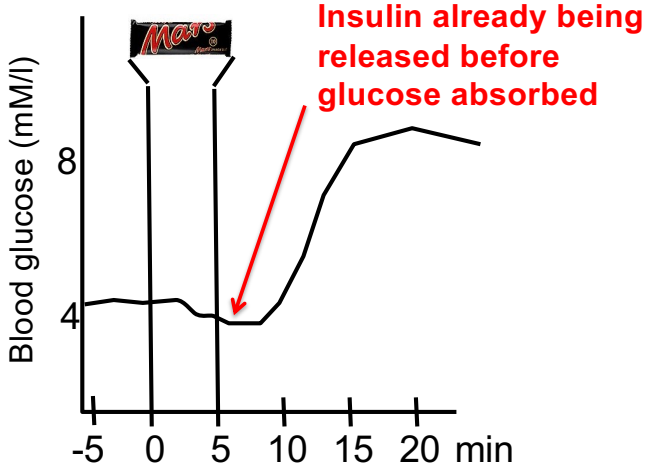
3. By the parasympathetic system



Control of insulin secretion by the parasympathetic system

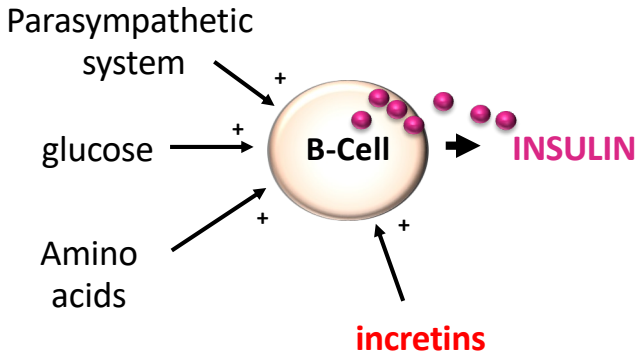
- Sight/taste/smell →
- Activation of vagal reflexes →
- Insulin secretion before food enters gut.
- Early insulin release helps prepare for the incoming glucose – prevents massive increase in glucose after meals.
- It can be detected (see graph). In the absence of absorbed glucose early insulin release may even cause a small dip in blood glucose.

Subjects have fasted before experiment.



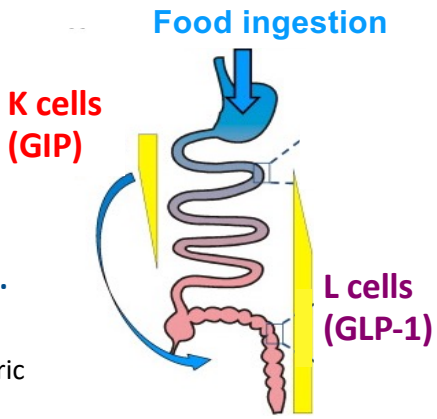
Control of insulin secretion

4. By incretins



Incretins

- Peptide hormones secreted into blood by enteroendocrine cells in the G-I tract
- Examples:
  - **GLP-1**: Glucagon-like peptide 1
  - **GIP**: gastric inhibitory peptide (or glucose-dependent insulinotropic polypeptide)
- **MAIN ROLES: ↑↑ insulin secretion, both in preparation for food being absorbed after eating.**
- Additional roles:
  - slow rate of nutrient absorption by reducing gastric emptying.
  - directly reduce food intake (CNS).
  - **GLP-1** (**BUT NOT GIP**) inhibit glucagon release.



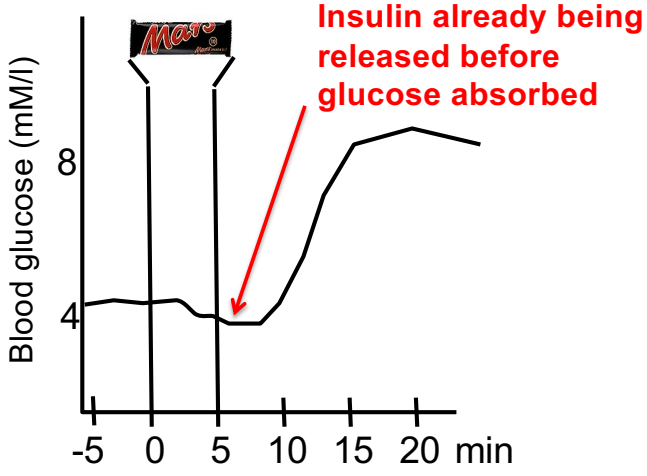
•**GLP-1**: Decreases glucagon secretion when glucose high but not when low. Helps avoid hyperglycemia.

•**GIP**: Stimulating glucagon release when glucose levels are low but not when high. Helps avoid

The presence of food in the gut triggers insulin secretion via incretin release

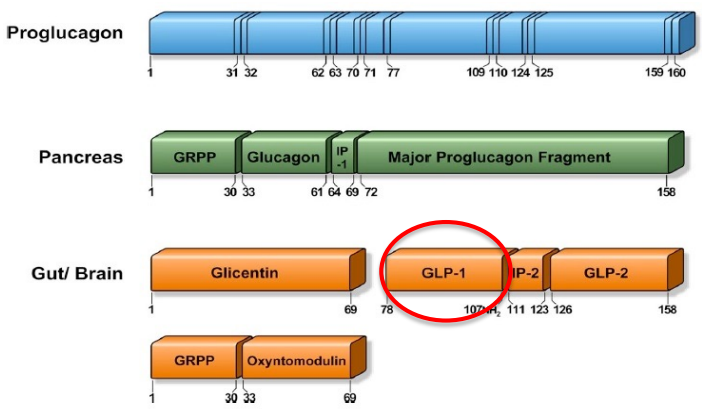
- Enteroendocrine cells respond to the presence of food in the gut (starting even before absorption) by releasing incretins.
- Incretins stimulate insulin secretion after eating but also before food is absorbed.
- Thus, they help prepare for the incoming glucose load.

Subjects have fasted before experiment.



Glucagon-like peptide 1 (GLP-1)

- Synthesized by entero-endocrine L cells and in the brainstem.
- Released when food present in gut.
- Decreases blood glucose (**incretin effect**)
- Very short half-life in blood (approx. 2 minutes)
- Stimulates insulin secretion (& inhibit glucagon release).



Why are incretins important?

In normal physiology …

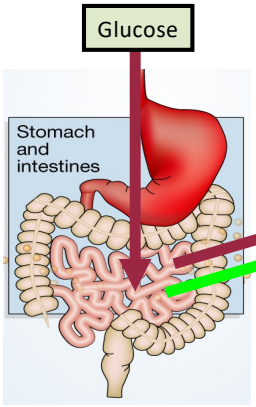
- Thanks to incretins, a little insulin is released into the blood even before glucose in the food is absorbed. Without incretin-induced insulin release, the body would not be prepared for the incoming glucose and it could suddenly become very high, which can be dangerous.
- In the presence of incretins, much more insulin is released in response to a meal. This is called the “incretin effect”.

In T2DM patients …

Drugs based on the incretin system have been developed

- Long acting GLP-1 analogues (eg exenatide, semaglutide (Ozempic®)
- Enzyme inhibitors - that inhibit the enzyme that breaks down GLP-1, thereby increasing circulating GLP-1 levels.

The Incretin Effect



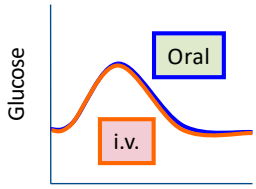
Glucose

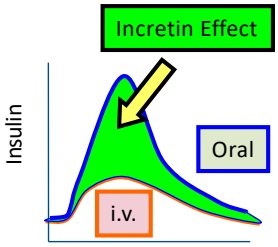
Pancreas

↑↑ Insulin

\+

GLP-1, GIP





1. Experimentally match i.v. glucose to that caused by a glucose infusion

2. Measure blood insulin

Oral glucose makes contact with GI tract and triggers incretin secretion
→ more insulin secreted after an oral glucose load than after i.v. infusion.
This difference = incretin effect

Nauck et al 1986 Diabetologia. 1986 Jan;29(1):46-52.

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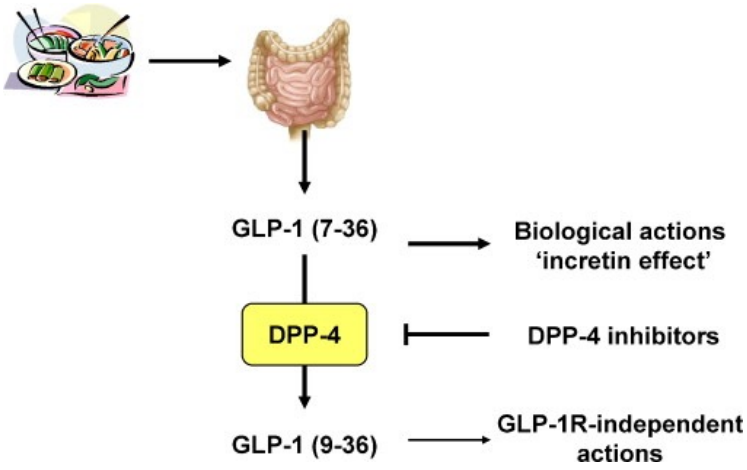
GLP-1 system → new drugs for diabetes (and obesity)

→ **GLP-1 long acting agonists** (eg Exenatide)

→ **DPP-4 inhibitors** (DPP-4 = enzyme inactives both GLP-1 & GIP). Mechanism: Prevents GLP-1 breakdown & prolongs GLP-1 half-life.



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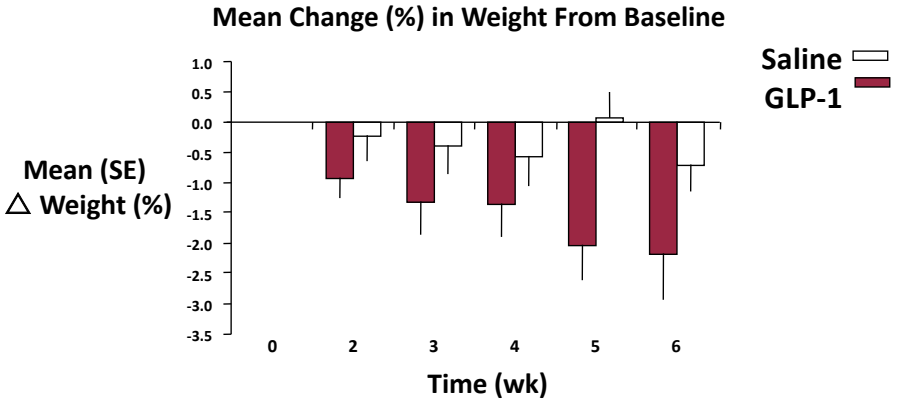
Incretin-based drugs are new treatments for type 2 diabetes (and cause weight loss)

Effect of 6-Week Continuous GLP-1 infusion on Mean Body Weight



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Topics

- Glucose homeostasis – the physiological challenge
- Glucostatic hormones that decrease blood glucose.
  - Insulin
  - Incretins
- **Glucostatic hormones that increase blood glucose**
  - **Glucagon**
  - **Adrenaline**
  - **Cortisol**
  - **Growth hormone**
- Other hormones

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Consequences of hyper- & hypoglycemia (i.e. too high and too low glucose)

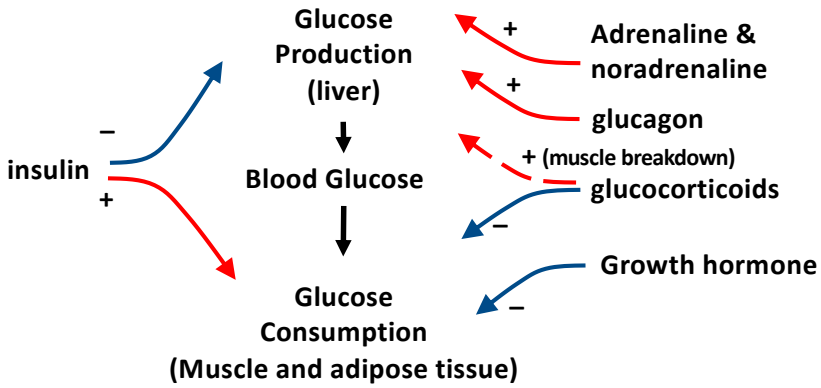
Blood glucose mmol/l	Result
>8	Exceeds renal threshold for uptake of glucose from pre-urine, diuresis (loss of glucose, water*, Na^+ and K^+ in urine)
5.5	Insulin secretion increases
4.6	Insulin secretion decreases
3.8	Increased secretion of glucagon, adrenaline and growth hormone
3.2	Cortisol secretion
2.8	Confusion
1.7	Weak, sweat, nauseous
1.1	Muscle cramps
0.6	Brain damage, death

*Acute fluid loss can become a medical emergency

Key glucostatic hormones- divergent roles

Glucagon, adrenaline, growth hormone promote glycogenolysis & gluconeogenesis.

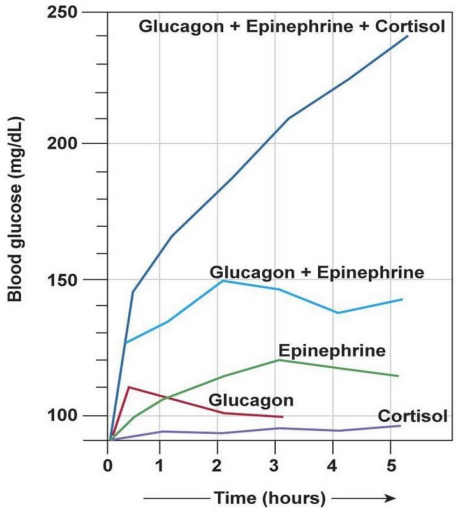
Glucocorticoids break down muscle (→ amino acids for gluconeogenesis).



Synergistic effects of anti-insulin hormones to increase blood glucose

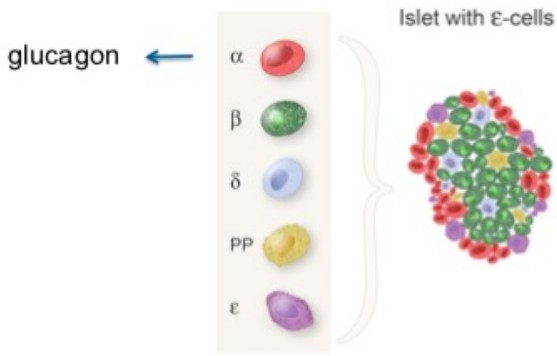
Cortisol has a "permissive role"

Permissive: allows a biological or biochemical process to occur



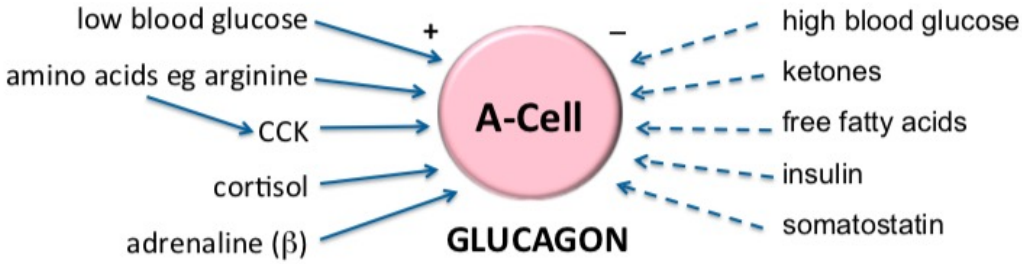
Glucagon

- **Where produced?** Peptide hormone, produced by alpha cells in the Islets of Langerhans of the pancreas



Glucagon

- **Where produced?** Peptide hormone, produced by alpha cells in the Islets of Langerhans of the pancreas
- **What stimulates & inhibits release**?

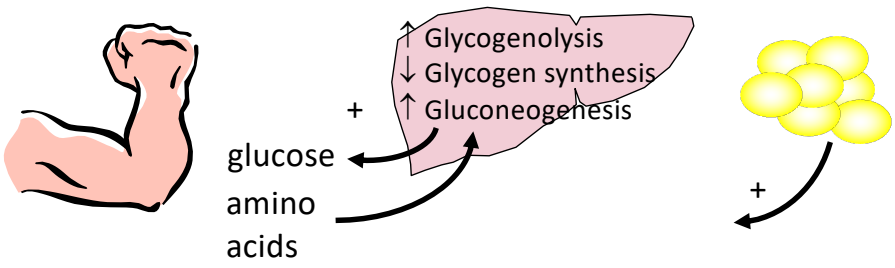


CCK=cholecystokinin

Glucagon

Important during initial stages of fasting

- **Where produced?** Peptide hormone, produced by alpha cells in the Islets of Langerhans of the pancreas
- **What stimulates & inhibits release**?
- **Primary actions:** increase blood glucose by **increasing glycogen breakdown** and **gluconeogenesis** in the liver



Glucagon

- **Where produced?** Peptide hormone, produced by alpha cells in the Islets of Langerhans of the pancreas
- **What stimulates & inhibits release**?
- **Primary actions:** increase blood glucose by **increasing glycogen breakdown** and **gluconeogenesis** in the liver.
- **The glucagon receptor is a G protein-coupled receptor.**
- **A life-saving safe injectable treatment for hypoglycemia.**

Glucagon

- Think of glucagon as the main hormone acting in the opposite way to insulin. It is important inbetween meals, helping to keep glucose levels up, by enhacing glycogen breakdown and gluconeogenesis.
- If you eat a diet low in carbs (eg LCHF – low carb high fat diet), you need to mobilize glucose from stores and generate new glucose. The substrates for gluconeogenesis are free fatty acids (from fat breakdown) and amino acids (from protein breakdown).

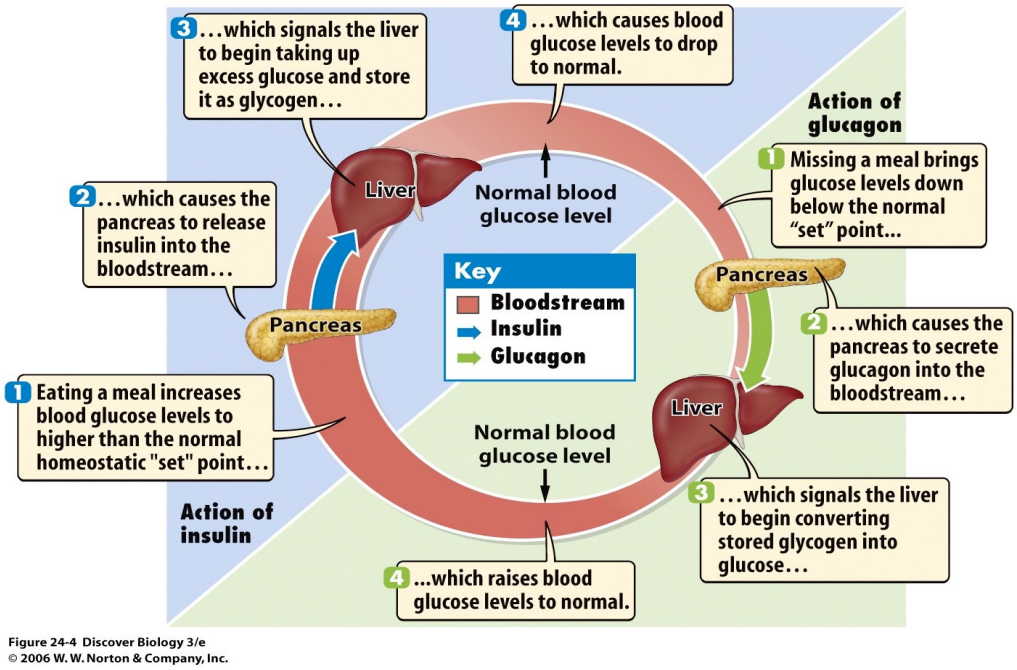


Figure 24-4 Discover Biology 3/e
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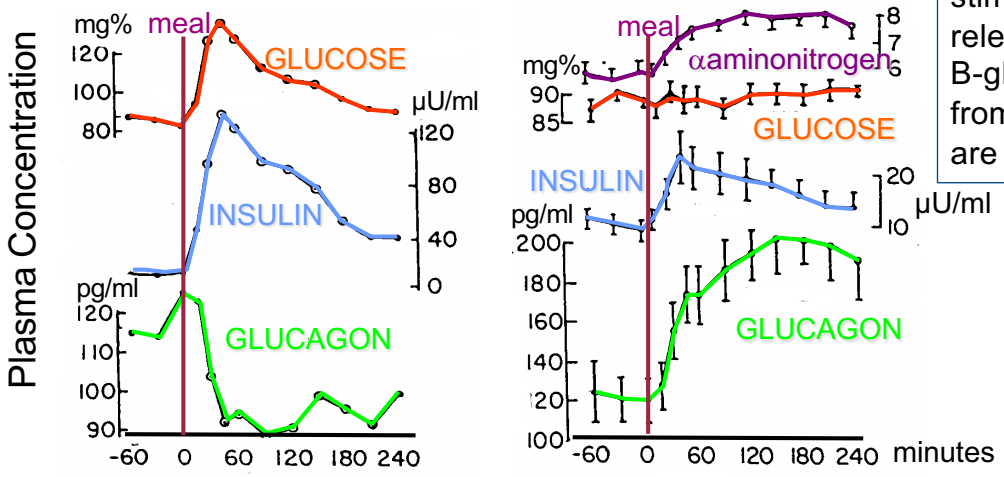
Effect of high carbohydrate and high protein meal on hormone secretion

Carbohydrate meal
(ie high glucose)

Protein meal
(ie high amino acids)



Both meals stimulate insulin release. Amino acids also stimulate glucagon release, which saves B-glucose levels from falling if carbs are low

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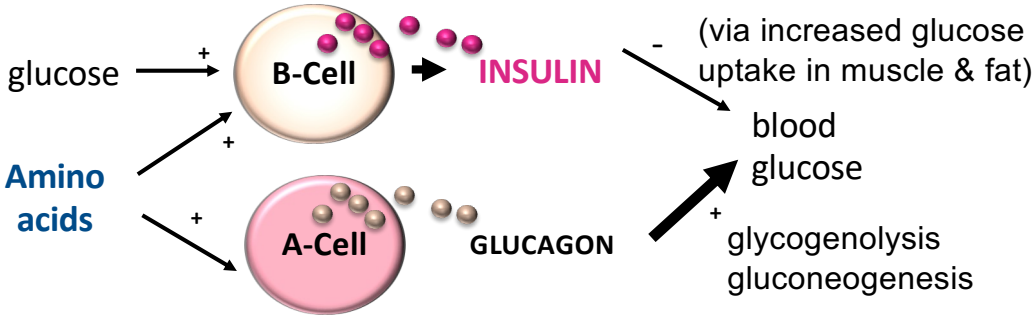
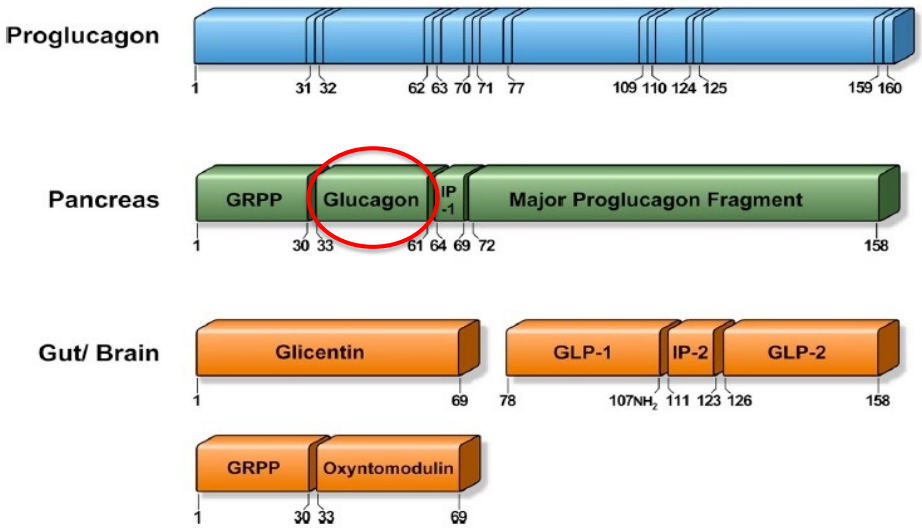
Control of insulin secretion

2. By amino acids

Although amino acids increase insulin secretion (which lowers blood glucose by increasing glucose uptake to fat and muscle), they also stimulate glucagon release (which promotes glycogenolysis and gluconeogenesis i.e. release and production of new glucose).



Pro-glucagon



Thus, although proglucagon can be found in many tissues, glucagon is only released from the alpha cells.

Fear- fright – flight. Need energy (glucose) fast
A role for adrenaline

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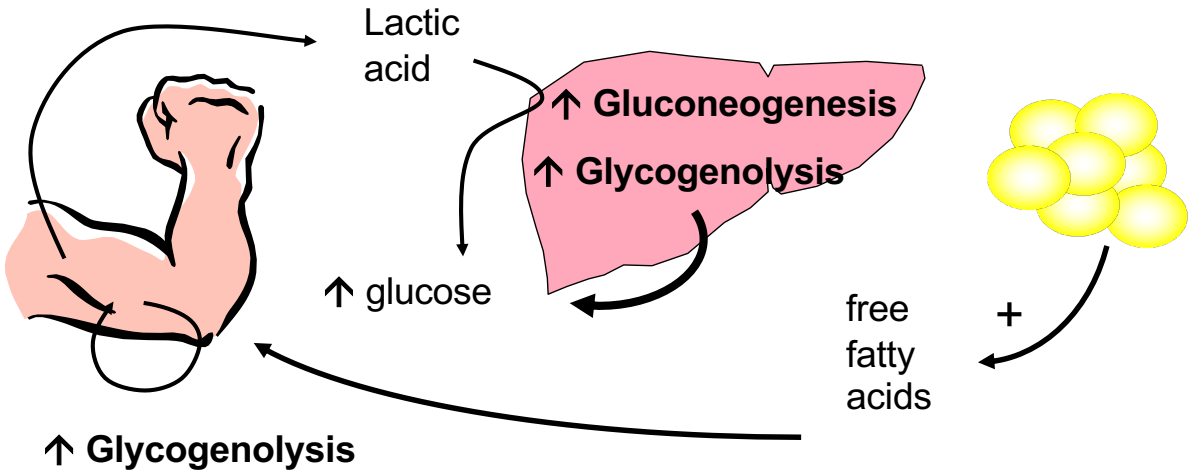
Adrenaline's effects on glucose homeostasis

Important during acute stress (minutes) eg exercise



Glycogenolysis, lipolysis

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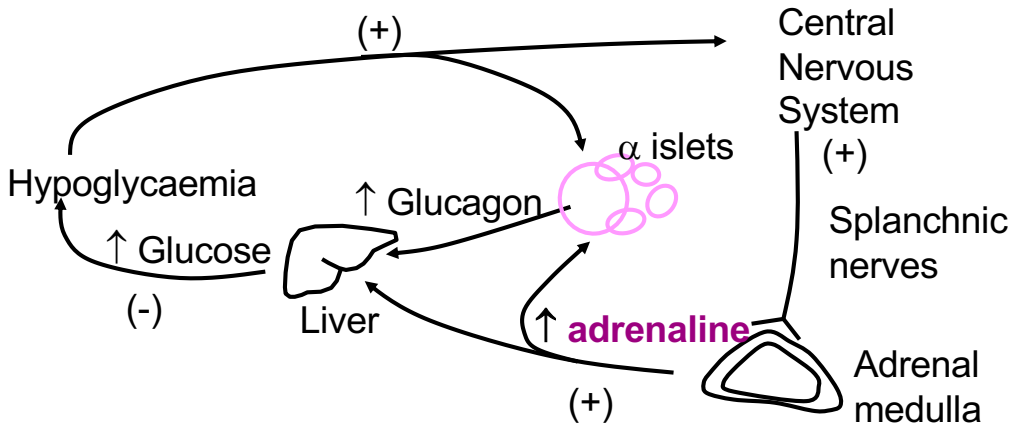
During acute stress adrenaline increases blood glucose

Stress from eg fear-flight-flight, hypoglycemia and cold exposure



Adrenaline

- in liver, it causes glycogenolysis (& gluconeogenesis to a lesser extent)
- It also stimulates glucagon release from the pancreas.

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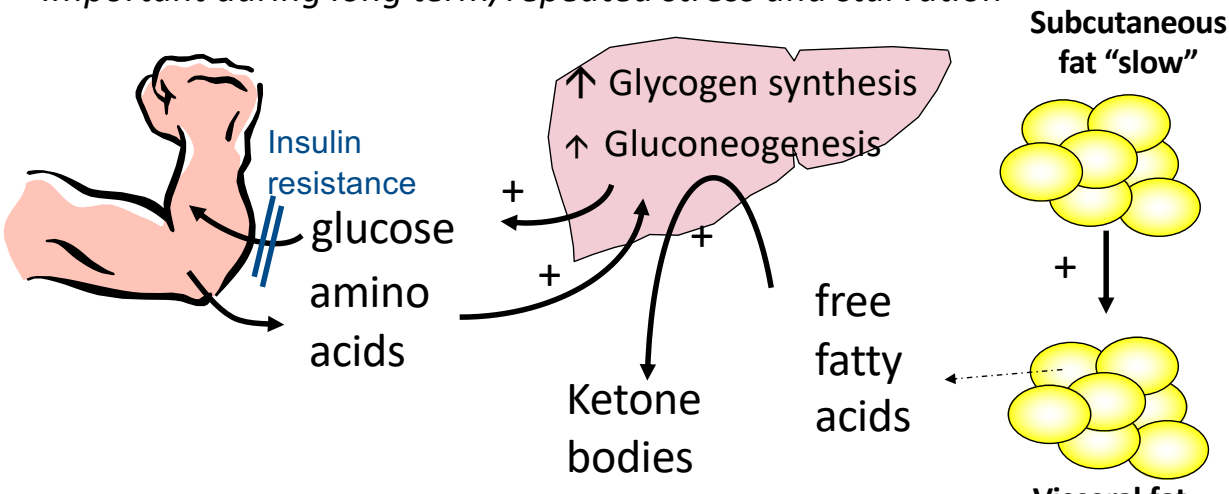
Glucocorticoids (from adrenal cortex)

Important during long term/repeated stress and starvation



Protein catabolism, glycogenesis, gluconeogenesis, ketogenesis, decreased glucose utilization

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Cortisol deficiency (eg Addison's disease)

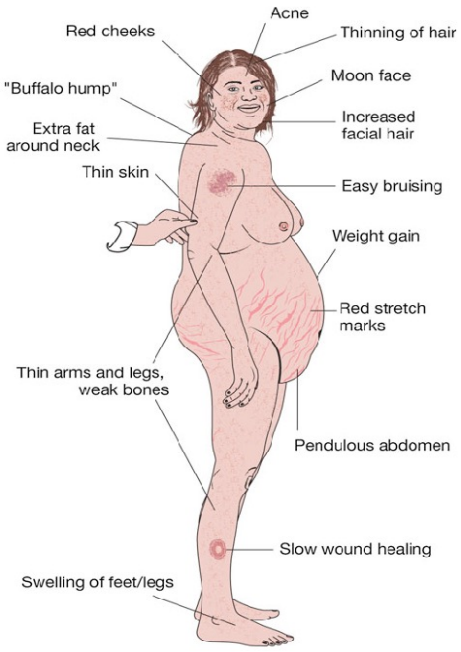
- **Blood glucose normal as long as food intake is maintained**.
- Fasting/starvation is life-threatening due to risk of hypoglycaemia
- Glycogen stores in liver and muscle become depleted.
- Becomes difficult to use other sources of stored energy eg protein & triglycerides.

JF Kennedy – probably the most famous person to suffer from this disease

Cortisol excess – Cushings disease

- Glucose tolerance* reduced by 80% - they have high blood glucose levels.
- 20% patients have type 2 diabetes.
- Glucocorticoids are required for glucagon to exert its gluconeogenic effect during fasting (permissive role).

**Impaired glucose tolerance (IGT) is a pre-diabetic state of hyperglycemia that is associated with insulin resistance and increased risk of cardiovascular pathology.*



Growth hormone (GH)

- Produced by the somatotrophs of the anterior pituitary.
- Release controlled by the hypothalamus, by negative feedback (via GH and IGF-1) and by ghrelin.
- Plasma membrane receptor. Dimerization.
- Actions: growth (anabolic) and metabolism (lipolytic, diabetogenic). Metabolic actions important when fasting or when blood glucose levels fall.

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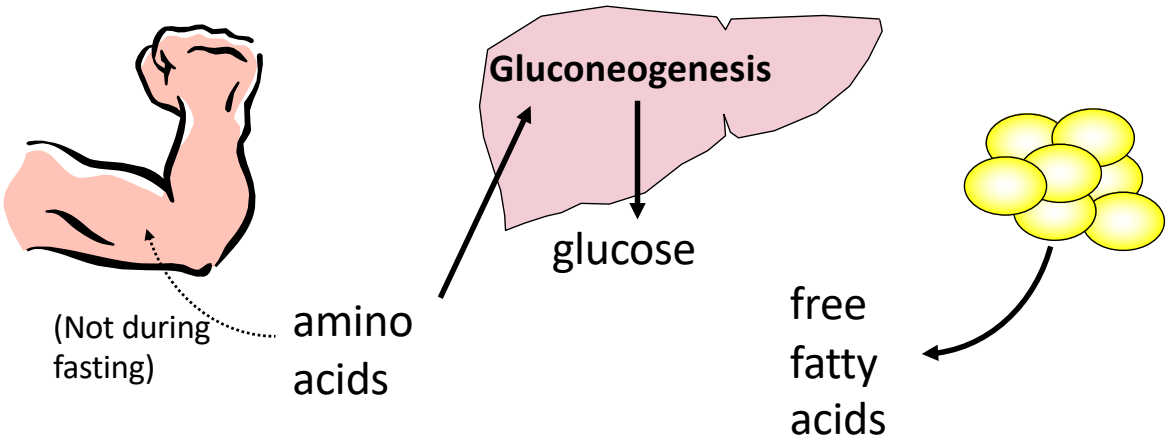
Growth hormone (GH) is diabetogenic, lipolytic (and anabolic)

Important when using fat rather than carbohydrate as an energy source (eg fasting).



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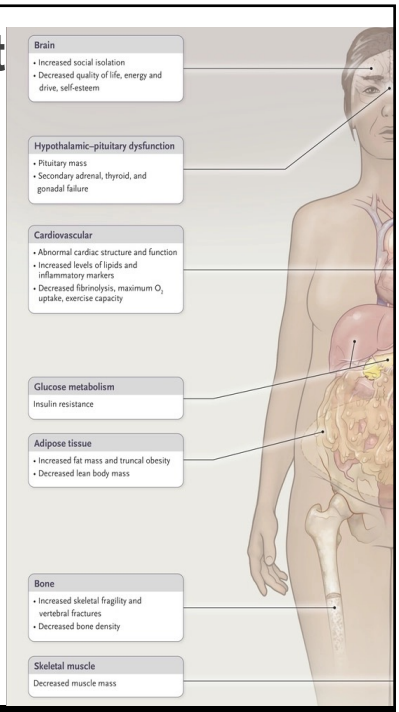
Metabolic profile of the GH-deficient patient

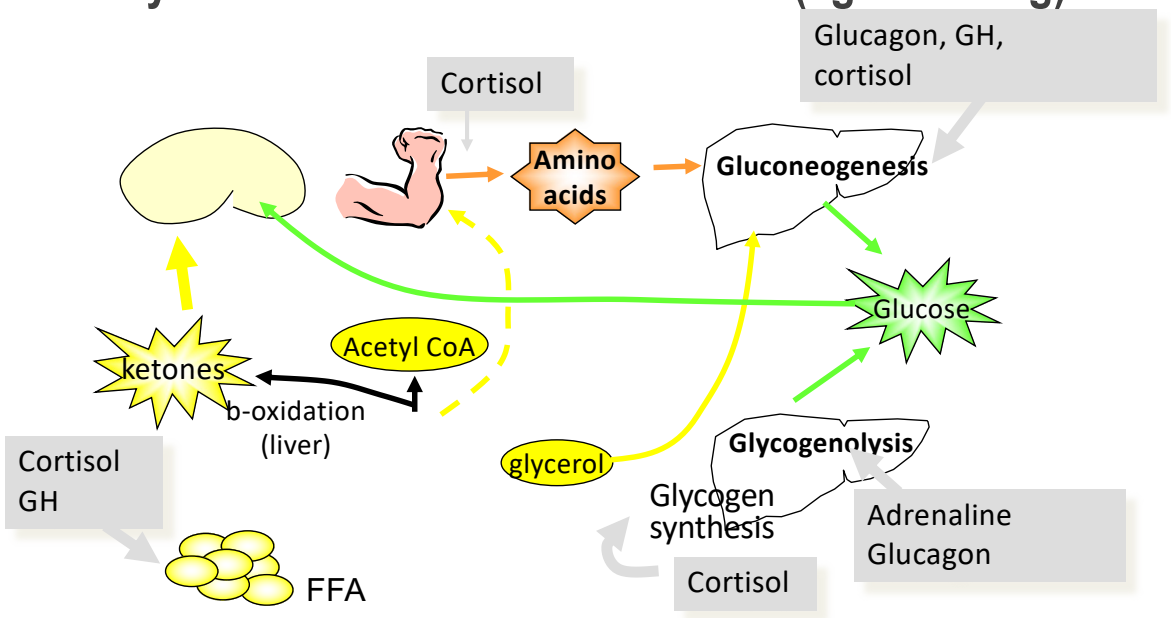
- ↑ central adiposity (apple-shaped)
- Insulin resistance (maybe secondary to the central adiposity).
- Liver: ↓ glycogen stores, ↓ gluconeogenesis
- Lipid profile: ↑ triglycerides, ↑ LDL-cholesterol, ↓ HDL-cholesterol, ↑ apolipoprotein b (promotes CV disease and arterosclerosis).



Metabolic profile of a patient with acromegaly

- Insulin resistance,
- GH blocks insulin's actions (inhibits phosphorylation of the insulin receptor and IRS-1)
- Mobilization of free fatty acids leading to further worsening of insulin resistance.
- Abnormalities overcome by either lowering of GH secretion or by blocking GH action.

Summary of anti-insulin hormone action (eg in fasting)



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Topics

- Glucose homeostasis – the physiological challenge
- Glucostatic hormones that decrease blood glucose.
  - Insulin
  - Incretins
- Glucostatic hormones that increase blood glucose
  - Glucagon
  - Adrenaline
  - Cortisol
  - Growth hormone
- **Other hormones**

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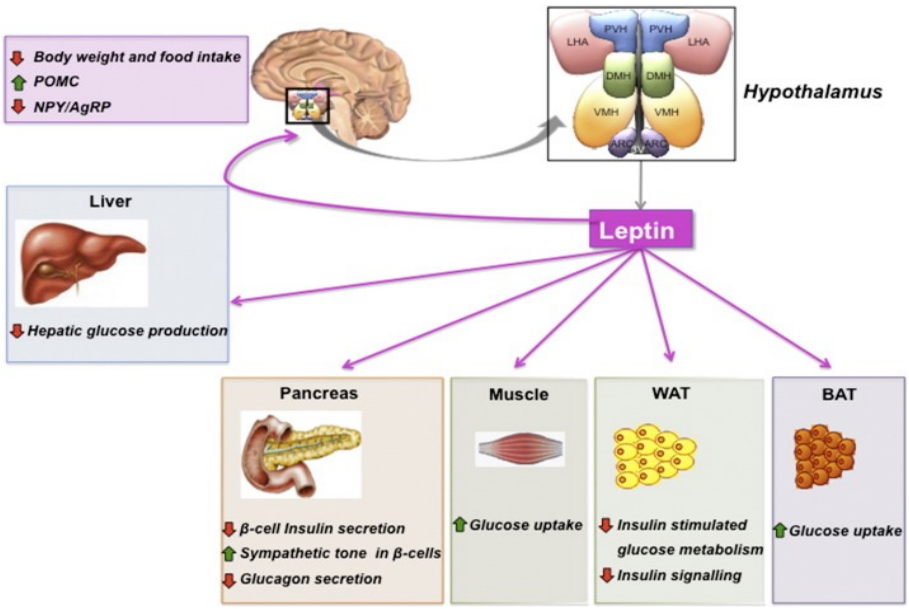
Leptin – beneficial effects to lower blood glucose



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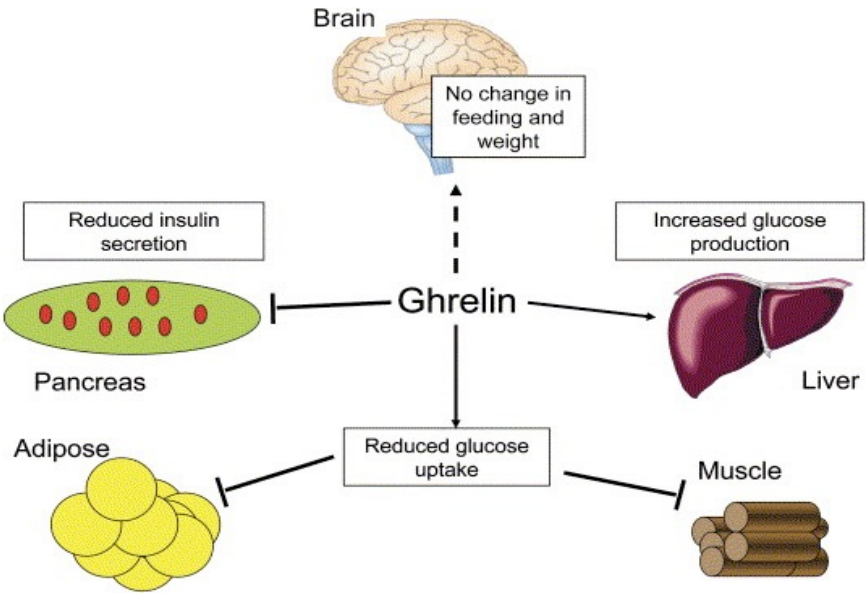
Ghrelin – improves (raises) blood glucose when fasting



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DIABETES MELLITUS: Topics

- Type 1, Type 1.5, Type 2 & gestational diabetes
- Symptoms and Diagnosis
- Insulin resistance and carbohydrate metabolism in diabetes.

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Why is diabetes mellitus an important disease?

- **Increases the most amongst all diseases!**
  - **Current worldwide**: 463 million, 50% 20-60 years old
  - **By 2035**: 592 million worldwide
  - **Current Sweden**: 4.8% of the population
- **A worldwide pandemic**
  - The increase in type 2 diabetes mellitus (T2DM): ”diabetes-causing lifestyle”
- **Developing countries – those affected even younger**
  - 50% type 2 diabetes occurs in those aged 40-59
  - T2DM is even the most common form in adolescents.

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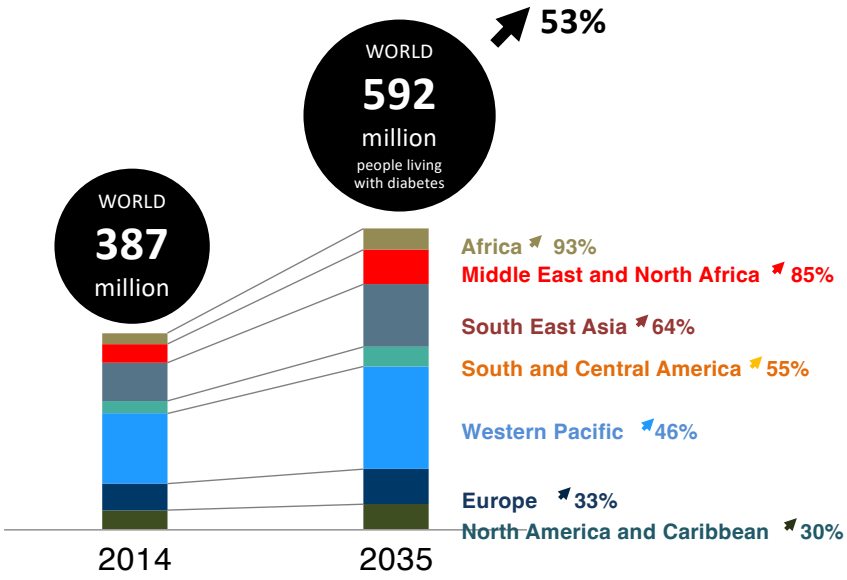

Contect from Anders Rosengren

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Type 1 Diabetes	• Because of autoimmune β-cell destruction • Usually leads to absolute insulin deficiency • Includes adult latent autoimmune diabetes
Type 2 Diabetes	• Caused by an advancing loss of sufficient β-cell insulin secretion • Insulin resistance is usually associated
Specific types of Diabetes due to other causes	• Monogenic diabetes syndromes (neonatal diabetes, maturity-onset diabetes of the young) • Exocrine pancreas diseases (pancreatitis, cystic fibrosis) • Drug- or chemical-induced diabetes (due to glucocorticoids, HIV/AIDS treatment, post organ transplant)
Gestational Diabetes Mellitus	• Diagnosed in the second or third trimester (and not prior to pregnancy), evident only during gestation

Most common. 90-95% all diabetes

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Kalle 12 years old

- Previously healthy
- Recent weeks - tired
- Very thirsty

  Polydipsi (↑ urine)
- Frequent urination

  Polyuria – osmotic diuresis
- Previously normal vision but now sits 1 metre in front of TV

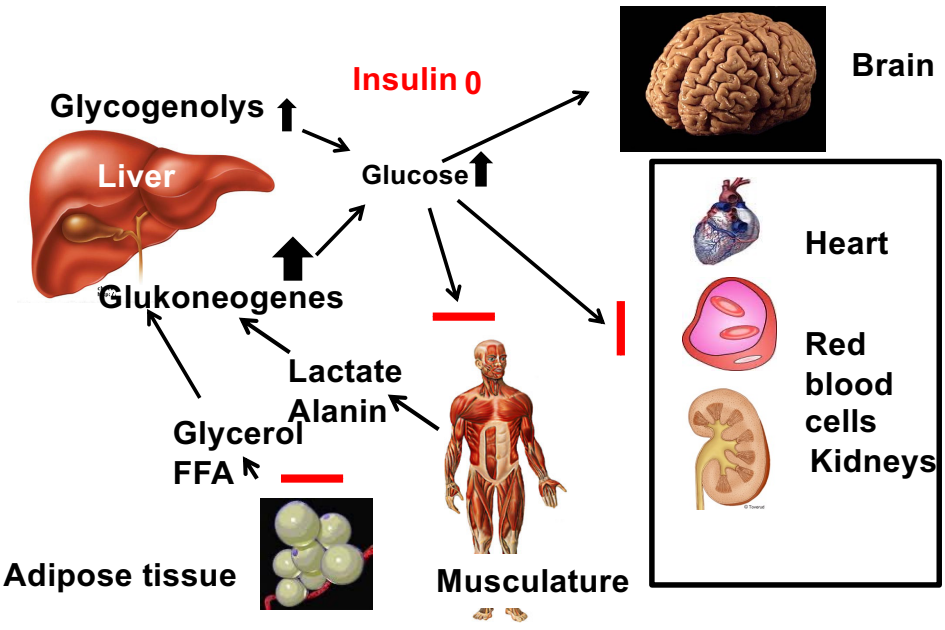
  Myopathy – eye swells (osmotic effect of glucose)
- Lost 3 kg in weight during 2 weeks (insulin deficiency → ↑ lipolysis & ↓ lipogenesis)

- Very tired (+ mucous membranes
- Acetone smell
- B-glucose: 22 mmol/l
- Urine teststick:

  ↑ glucose (fungal infections, genital itching)

  ↑ ketones
- Stomach pain/vomiting (ketoacidosis, hyperosmolar hyperglycaemic syndrome)
- Serum insulin: 0 ng/mL C-peptide: 0 nmol/L

Glucose metabolism in diabetes



Even type 1 diabetes mellitus (T1DM) is increasing

- 10% of all diabetes is type 1.
- T1DM increasingly common. Almost 30% ↑↑ over past 30 years. Number of sick children with T2DM aged 0-14 has ↑↑ by 3% every year since 1980.
- There is a clear tendency for T1DM to affect younger children. It is not uncommon for 1-2 year olds to become ill.
- Just over 1% of all children born in Sweden have T1DM (about 700 children and adolescents develop the disease each year)
- Around 98,000 children are affected by T1DM each year in the world

Type 1 diabetes mellitus (T1DM)

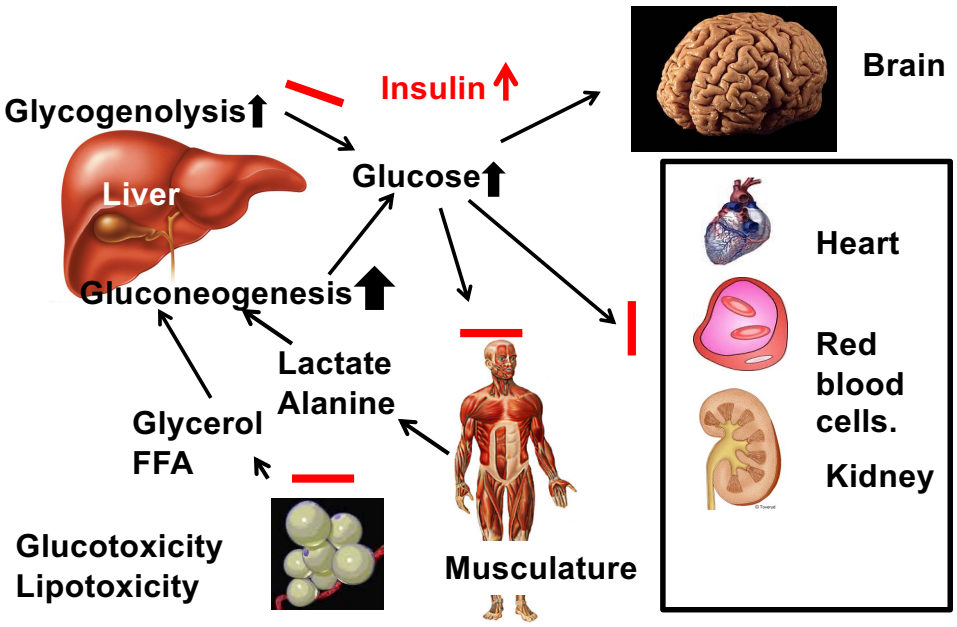
- Insulin-producing β-cells destroyed due to auto-antibodies.
- **90% T1DM have auto-antibodies**: directed against substances in the beta cells: **insulin**, **GAD** (glutamic acid decarboxylase) and **IA-2** (tyrosine phosphatase).
- **Theory:** a certain type of gene + triggering factor is required (e.g. viruses, chemicals or other environmental factors).
- 60% of the hereditary risk of T1DM is in the **HLA (human leucocyte antigen) system** (that labels cells as belong to the body or to be rejected).
- Risk genes are common in the population (about 20%) but only 7% (of this 20%) get T1DM.
- Autoimmune disease? – Limited evidence for this. Inhibition of T-cell mediated autoimmunity in newly infected patients has failed.
- Inflammatory disease affecting the entire pancreas, most important clinical symptoms come from the loss of insulin producing cells.

Ove, 58 år

- Fatigue, dizziness, depression
- Mother with diabetes
- Weight 126 kg
- Waist circumference 103 cm
- BMI 33 kg/m^2
- Blood pressure 185/100
- Heart, lungs, abdomen – no problem.
- Wound infection knee

- B-glucose: 12 mmol/l
- Urine teststick glucose: ++
- Ketones: negative
- Serum insulin (ref. 68-245 ng/mL) 345 ng/mL
- LDL-cholesterol ↑
- HDL-cholesterol ↓
- High triglycerides ↑

Glucose metabolism with diabetes



Glucotoxicity (High blood glucose toxic)

→ ↓ ability of β-cells to release enough insulin,

→ ↓ ability of peripheral target cells' to respond to insulin.

→→ a vicious cycle that accelerates hyperglycemia.

Lipotoxicity (High lipid levels toxic)

β-cell damaged. ↓ insulin release.

Peripheral target cells, e.g. vascular endothelium, muscle and liver cells: impaired function and ↓ insulin sensitivity.

Can be counteracted by metabolic control mainly diet and exercise but also lipid-lowering pharmacological treatment.

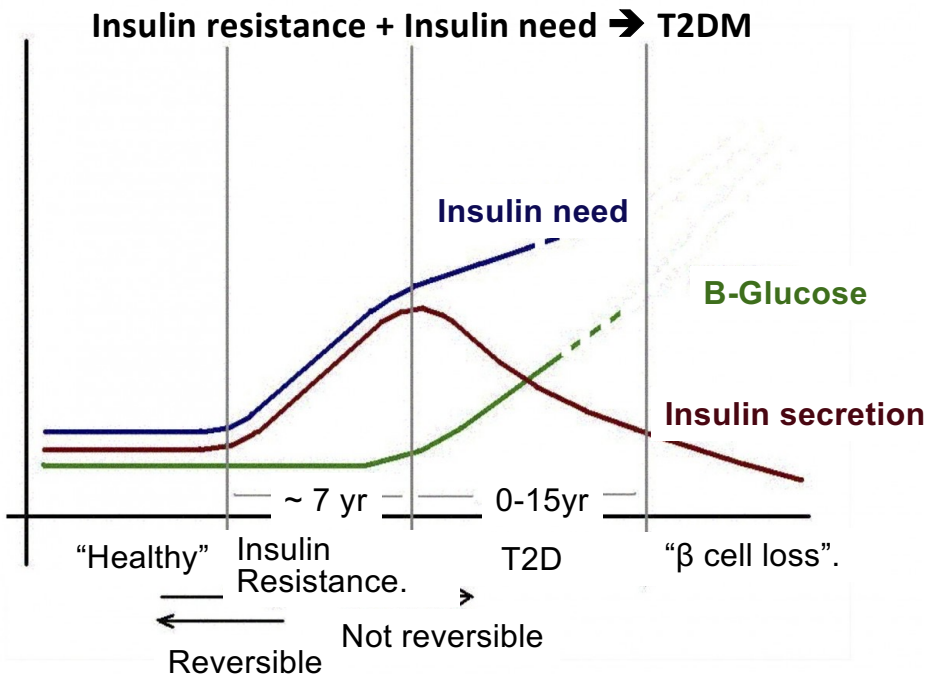
Type 2 Diabetes Mellitus (T2DM)

- **Insulin resistance and insulin deficiency**
- Heterogenous illness with many different potential causes
  - 80% patients are overweight/obese (BMI > 30 kg/m^2)
  - Insulin resistance increases with increasing obesity and abdominal obesity
- Clear association between physical inactivity and increased risk of T2DM.

Genes and environment work together

- T2DM highly hereditary. If a parent has T2DM, the children have a 40% risk. They have a 70% risk of falling ill during their lifetime.
- Heredity in T2DM complicated - difficult to identify risk genes. Polygenetic inheritance (GWAS> 120 loci strongly linked but explains only 20% of the disease). "A genetic nightmare"!
- Genetics (several genes in collaboration) + lifestyle contribute to the risk of developing the disease





Clinical characteristics of type 1 and type 2 diabetes

Type I DM	Type 2 DM
Lean or over weight	Overweight ~ 80%
Ketosis inclined	No ketosis
Symptoms for weeks before diagnosis	Symptoms for months before diagnosis
Age onset <40 år	Age onset typically >40 år
Heredity 10 %	Heredity common
HLA antigens precede disease in 90-95 % cases	HLA antigens precede disease in 60 % cases (as in normal population)
Islet cell antibodies at onset positive in about 70-80 % cases	Islet cell antibodies at onset - negative

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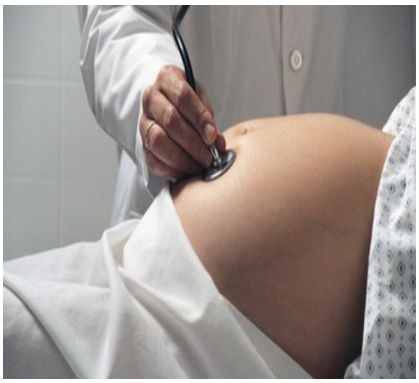
Gunilla 37 years old

- Presented as sweating and frequent urination
- 28th week of gestation
- Heredity: Mother with DM
- B-glucose: 12 mmol / l
- Urine test stick glucose: +++
- Ketones: 0
- U-Nitrite: +
- Serum insulin (ref. 68- 245 ng / mL) 675 ng / mL



Referral to a diabetes nurse and nutritionist

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Gestational diabetes Mellitus GDM

Defined as pathological glucose tolerance detected during pregnancy. After termination of pregnancy, the glucose metabolic disorder is usually normalized.

If not, "reclassification" to type 1 or type 2 diabetes occurs

0.8–4.3% of all pregnancies in Sweden

Women with GDM are a heterogeneous group (with varying degrees of deviation in glucose tolerance) that developed T2DM

Insulin resistance is more pronounced than in a normal pregnancy, and cannot be entirely explained by co-occurring obesity

The main cause is a defective insulin response that cannot keep up with increasing insulin resistance during pregnancy

GDM usually runs asymptomatically, requiring screening

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Fredrik 37 years old

- Presented with frequent urination. Prostate?
- 70 kg BMI 23 kg/m^2
- Blood pressure, heart, lungs, abdomen – no problem.
- B-glucose: 13 mmol/l
- Blood fats u.a.
- Urine teststick glucose: +++
  ketones: 0
- Serum insulin (ref. 68-245 ng/mL) 130 ng/mL

Type 2 diabetes?

Metformin
Lifestyle advice
Referral to diabetes nurse and dietician

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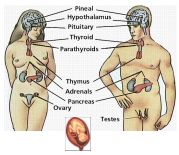
Fredrik 8 months later

- Tired & frquent urinating
- Acetone smell
- 66 kg
- Blood pressure, heart, lungs, abdomen – no problem.
- B-glucose: 17 mmol/l
- Urine teststick glucose: +++
- Ketones: +++
- Serum insulin: 0 ng/mL
- C-peptid: 0 nmol/L
- Islet cell antibodies (GAD) positive

Type 1 diabetes?

LADA (Latent Autoimmune Diabetes in Adults) between type 1 & type 2 diabetes - type 1.5 diabetes

- An autoimmune disease with islet cell antibodies (cf. T1DM) but usually older at the onset of illness. The disease course is slower and milder with preserved insulin production for an extended period of time. Similar in time to the debut of T2DM.
- require insulin treatment sooner or later. Important with proper diagnosis in the beginning so that insulin needs are met a.s.a.p. and not delayed.
- About 10% of all people with diabetes after the age of 35 have LADA (ie almost as common as T1DM)
- LADA was first described at the beginning of the1980s.



Summary Diabetes

- Diabetes is a worldwide pandemic and the problem is increasing.
- Type 1 and Type 2 are the most common forms
- The impact of carbohydrate metabolism is insulin deficience and insulin resistance
- Insufficient insulin secretion relative to insulin need → Type 2 DM