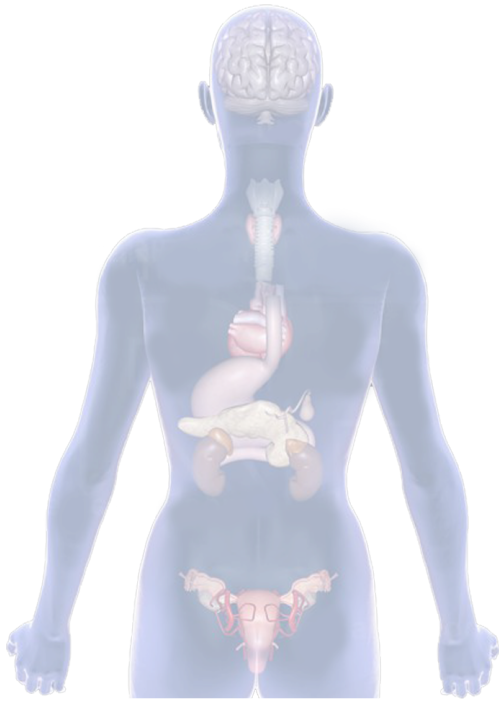
Physiology 435 team

#14 &15: physiology of the pancreas & insulin

Glucose metabolism terms:

- Gluconeogenesis - Synthesis of glucose from noncarbohydrate precursors, Lactic acid, glycerol, amino acids, liver cells synthesis glucose when carbohydrates are depleted.
- Glycogenesis - Formation of glycogen, glucose stored in liver and skeletal muscle as glycogen, important energy reserve.
- Glycogenolysis – breakdown of glycogen (polysaccharide) into glucose molecules (monosaccharide)
- Glycolysis - the breakdown of glucose into pyruvate by cells for the production of ATP



Important
Males notes
Females notes
Extra

Revised by
خولة العماري & هشام الغفيلي

Resources: 435 female's slides+ 435 Male's slides
Editing file: click Here

The pancreas

The pancreas:

The pancreas is a triangular gland, located behind the stomach (Strategic location)
It has both exocrine and endocrine cells

- **Exocrine:** Acinar cells produce an enzyme-rich juice used for digestion (exocrine product)
- **Endocrine:** Pancreatic islets (islets of Langerhans), which are 1-2 million islets in number, produce hormones involved in regulating fuel storage and use (glucose, lipids, and protein metabolism), they are highly vascularized (10-15% of blood flow) and innervated by both sympathetic and parasympathetic neurons.

Islets of Langerhans:

Cell type	Products (total=100%)
Beta (β) cells	produce insulin (60-70%)
Alpha (α) cells	produce glucagon (20-25%)
Delta (δ) cells	produce somatostatin (GHIH) (5-10%)
F cells (gamma γ or PP cells)*غير مهم	produce pancreatic polypeptide (5%)

*which inhibits pancreatic exocrine secretion of enzymes and bicarbonate.

Paracrine Signals in the Islets: *Boys' slides only

1. **Somatostatin inhibit *Alpha cells (Glucagon)* and *Beta cells (Insulin).*** Somatostatin always acts as inhibitor
2. **Glucagon stimulate *Beta cells (Insulin)* and *Delta cells (Somatostatin).***
3. **Insulin inhibit *Alpha cells (Glucagon)***

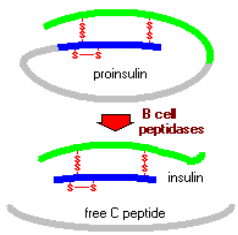
Insulin

Overview and structure

- Hormone of **nutrient abundance** (i.e. secreted after food intake) اسمه هورمون الوفره مايفرز في حاله المجاعه, يفرز اذا عندي وفره من المغذيات (الجلوكوز , الامينو اسيد,الدهون)فياخذها من الدم ويدخلها للخلايا زياده على ذلك يمنع انها تطلع من الخلايا

(eg:inhibits the glycogenolysis,lipolysis & inhibits the catabolism of amino acid)
in case of increase of nutrients concentration insulin order to the brain to stop food intake

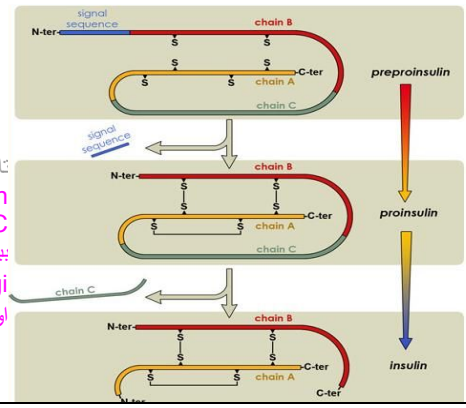
- A protein hormone consisting of **two** amino acid chains linked by **disulfide bonds**
- Synthesized as part of proinsulin (86 AA) and then excised by enzymes, releasing functional insulin (51 AA) and C peptide (29 AA) تحت تفاصيل احسن
- Has a plasma half-life of 6 minute = Short half-life.



Synthesis of insulin

DNA (chromosome 11) in β cells → mRNA → **preproinsulin** (signal peptide, A chain, B chain, and peptide C) → proinsulin → insulin

تابعو الصورة وانتم تقرون هالكلام:اول شي الانسولين بيتصنع داخل كروموسوم 11 في البيتا سيل ك
signal peptide, A chain, B chain, and عباره عن اربع سلاسل) preproinsulin
ثم يدخل ER اول مايدخلها بتتكسر السيقنال ببيتايد وايضا peptide C) بترتبط A chain &B chain
يبعض disulfide bonds linked by ويصير اسمه proinsulin بعدها ←
proinsulin is then packaged into vesicles in the Golgi
اول ماتدخل الجولجي بتتكسر ال peptide C هنا نسميه انسولين وهذا الي يعتبر الاكتف



secretion of insulin

Ca entrance promotes? Insulin secretion

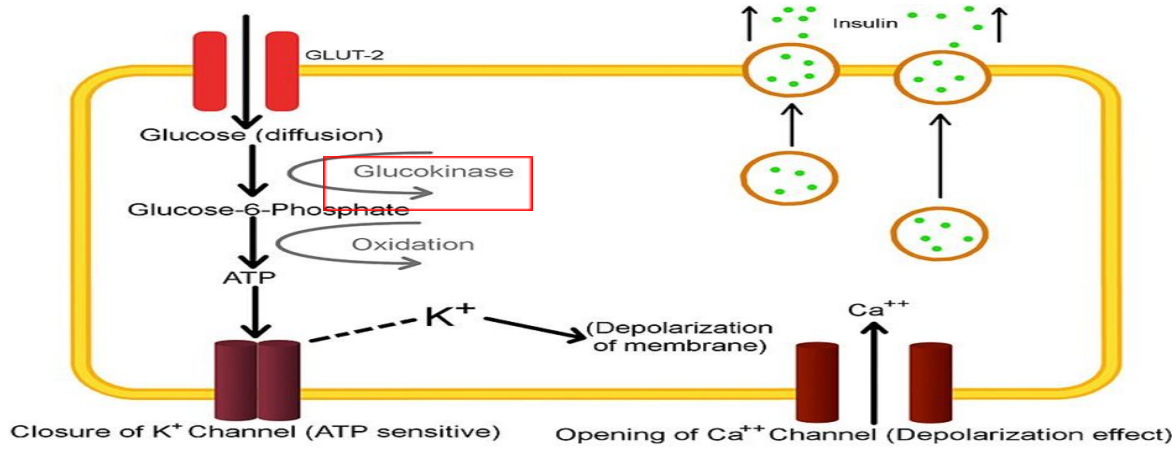
الصورة هذه مهمة مرة، ولازم تفرقون بينها وبين السيكريشن اوف قلوكاقون

Glucose is the primary stimulator of insulin secretion

- Insulin synthesis is **stimulated** by **increase blood glucose** or **feeding**, and **decreased** by **decrease blood glucose** and **fasting**.
- Threshold of glucose-stimulated insulin secretion is 100 mg/dl
- Glucose **rapidly increase the translation** of the insulin mRNA *(to form new proteins)*

and **slowly increases transcription** of the insulin gene *(in the cell nucleus)*

كيف يدخل الجلوكوز للبيتا سيل وكيف يؤدي الى افراز الانسولين من البيتا سيل؟تابعو الصورة وانتم تقرون هالكلام: اول شي عندنا ناقل على سطح الخلية بيتا اسم هالناقل GLUT2 اذا في جلوكوز كثير بالدم بيدخل الجلوكوز عبر الGLUT2 الى داخل الخلية اول مايدخل الخليه بيرتبط مع فوسفات كأنه يصيرله ترابتق نحبسه داخل الخليه عشان مايسلل للخارج الانزايم المهم الي يخلي الجلوكوز يرتبط بالفوسفات اسمه **GLUCOKINASE** (هذا الانزايم مره مهم يعتبر **rate limiting step** لان بدونه مانقدر نحبس الجلوكوز داخل الخليه وبتسلل للخارج ومراح ينفرز الانسلين),اول مايتكون الGlucose-6-phosphate بيتكون كمية كبيرة من ال ATP داخل الخلية تكون الATP يعمل على اغلاق بوابة K leakage channel مانعا البوتاسويم انه يطلع برا فتتراكم كمية كبيرة من البوتاسيوم داخل الخلية مما يؤدي الى زيادة شحنة الخلية الموجبة ,زيادة شحنة الخلية الموجبة تؤدي الى depolarization of the membrane مؤديا الى فتح بوابة اسمها Ca voltage gated channel اول ماتنفتح هذي البوابة بيدخل الكالسيوم الى داخل الخلية دخول الكالسيوم للخلية يعمل على تحفيز افراز الانسولين (الي قاعد في فزيكلس) الى خارج الخلية ثم الى الدم :)



Regulation of insulin secretion

Stimulators of insulin secretion:

1) ↑ **Blood glucose concentration (major Control)** اهم اهم واحد
2) ↑ Blood amino acid conc. ابغاكم تعرفون ان الامينو اسيد يرفع الانسولين بس بنسبة قليلة فلو اكلتي بروتين بلحاله ماراح يرفع الانسولين بنسبه كبيره , لكن لو اكلتي بروتين وجلوكوز بيحفز افراز كمية كبيرة من الانسولين
3) ↑ Serum free fatty acids
4) ↑ Serum ketone bodies

اذا زاد احد هذي الاربعه الي فوق بالدم يتحفز الانسولن وياخذها من الدم ويحطها بالخلايا

5) Food intake, which increases 2 other stimulators:

A. Gastrointestinal hormones: هذي هورمونات تفرز اذا دخل اكل للجي اي ,في حالة الوفره نحتاج هورمون الوفرة يتحفز ويدخل المواد المغذيه داخل الخلايا

- Gastroinhibitory peptide (GIP) -
- Glucagon - Gastrin -
- Cholecytokinin (CCK) - Secretin -
- Vasoactive intestinal peptide (VIP) -

لو شخص اخذ اورال حلوكوز وثاني اخذ IVالجلوكوز مين بيصير عنده الانسولين اعلى بالدم؟ الي اخذ اورالي لانه حفز الانزيمات الهاضمة بالاضافه الى ارتفاع الجلوكوز بالدم كلها تعمل على تحفيز افراز الانسولين

B.The autonomic nervous system:

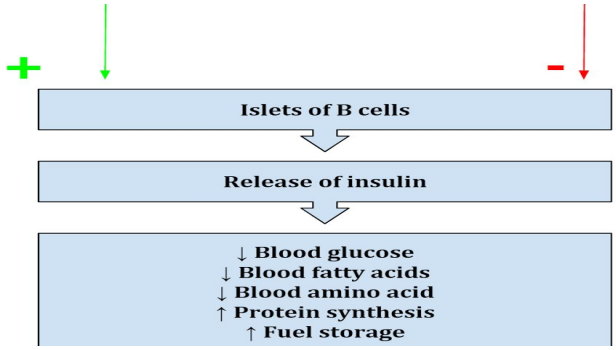
- **Parasympathetic** stimulation
- Epinephrine (β -receptor) بتستغربون كيف ابنفرين يحفز الانسولين احنا بحالة سترس نحتاج جلوكوز ؟؟ اول شي لاحظو انها بيتا ريسبتور ثانيا اقرو النوت الي بالزهر يمين عشا تعرفون التفسير

Inhibitors of insulin secretion:

1) ↓ **Glucose** اهم اهم واحد
2) ↓ Amino acids
3) ↓ Free fatty acids
4) **Hormones:**
   - Somatostatin (GHIH)
   - Epinephrine (α - receptor)
5) **Sympathetic** nervous system

NOTE:Sympathetic NS generally inhibits insulin release. When it acts on α receptors it inhibits insulin secretion but when it acts on β receptors it stimulates insulin release, however β cells have more α receptors which makes the net result of SNS: inhibition of insulin secretion

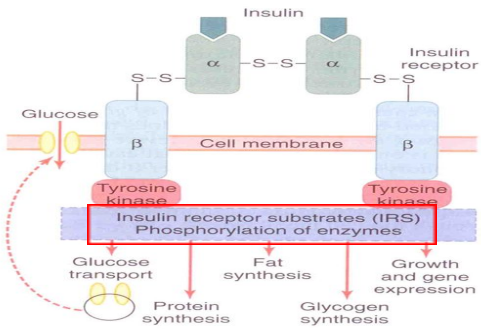
- لاحظوا ان ال Glucagon يحفز افراز الInsulin
- الانسولين قليل خاتمة يقلل افراز ال Glucagon.



Insulin receptor

- The insulin receptor is a **transmembrane receptor**
- Belongs to the large class of **tyrosine kinase receptors**
- Made of **two alpha subunits** and **two beta subunits**

Insulin binds to α receptor>autophosphorylation of β receptor>activation of tyrosine kinase>activates IRS>الحين بيدأ الايفيكتس للانسولن يظهر زي تصنيع البروتين والفات والجلايكوجين وتحفيز النمو اضافه لذلك يقوم ياخذ نواقل الجلوكوز **(GLUT4)**
ياخذها من السايتوبلازم ويحطها على سطح الخليه عشان يسمح للجلوكوز انه يدخل من الدم للخلية



Actions of insulin

Action of insulin in general:(+) cell growth الانسولين له دور مهم بالنمو مثل اهمية هورمون النمو بالنمو
MAIN ACTION of insulin: Increase transport of **glucose, amino acids, K+** into **insulin-sensitive cells**(Liver, Muscle and Adipose tissue).

Action of insulin on insulin-sensitive cells

مين هي الخلايا الي تعتمد على الانسولين عشان يدخل الجلوكوز داخلها insulin-sensitive cells?? Liver,Muscle & Adipose tissue.
البرين مايحتاج انسولين عشان تدخله الجلوكوزو الجلوكوز تدخل للبرين دايركت بGlut3

Liver:

(+) protein synthesis
(+) lipid synthesis
(-) ketogenesis[1]
(+) glucose entry (+ GLUT**2** transporters)
(-) gluconeogenesis
(-) glycogenolysis.
(+) glycogen synthesis
(↑ *Glucokinase*)
(+) glycolysisالانسولن يبي يتخلص من الجلوكوز بكل الطرق الممكن: يدخله للخلية ,يكسره , يمنع تصنيعه

Muscle:

(+) amino acid uptake
(+) protein synthesis in ribosomes
(-) protein catabolismمره مهم
(-) release of gluconeogenic amino acidsيمنع اخراج الامابنو اسد الي تساعد على عملية الجلوكونيوجنسس
(+) ketone uptake
(+) glucose entry (+ GLUT**4** transporters)
(+) glycogen synthesis
(+) K uptake

Adipose tissue:

(+) glucose entry (+ GLUT**4** transporters)
(+) glycerol phosphate [2]synthesis
(+) fatty acids synthesis
(+) triglyceride deposition
(+) lipoprotein lipase[3]يكسر البروتين الي عالق بالدهون عشان يدخل الدهون من السيركيوليشن للاديبوسايت يعني يشيل VLDL and Chylomicrons من السيركوليشن.
(-) hormone-sensitive lipase[4]يثبط الانزايم الي يطلع الليبد من الاديبوسايت , فالانسولين يحط الليبد داخل الديبوسايت
(-) lipolysis
(+) K uptake
لاحظتو تأثيره على الليبد يسوي أي شي عشان يشيل الليبد من السيركيوليشن ويدخلها للاديبوسايت(يعني يسمن)

Actions classified by duration

Rapid (seconds):

(+) transport of glucose, amino acids, K+ into insulin-sensitive cells

Intermediate (minutes):

(+) protein synthesis
(-) protein degradation
(+) glycolytic enzymes and glycogen synthesis
(-) phosphorylase[5] and gluconeogenic enzymes

Delayed (hours):

(+) mRNA for lipogenic and other enzymesاي شي يدخل داخل نواة الخلية يتطلب وقت

Glucose transport

- GLUT1 (erythrocytes - brain)
- GLUT2 (Liver - pancreas - small intestine - kidney) mnemonic:**beta cell LIKES** Glut2 عشان 2تعرفون اماكن تواجد الجلوت(**beta cell**=pancreas,**L**=liver,**I**=intestine,**K**=kidney)
- GLUT3 (brain)البرين يدخله الجلوكوز دايركت مايحتاج انسولين
- **GLUT4** "which is insulin sensitive transporter" (muscle - adipose tissue) نسالكم في الامتحان شو هو most insulin sensitive receptor! الاجابة دايما كل ماهو GLUT4 :))

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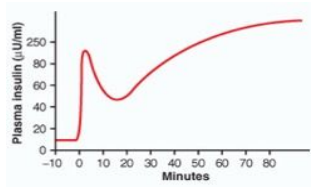
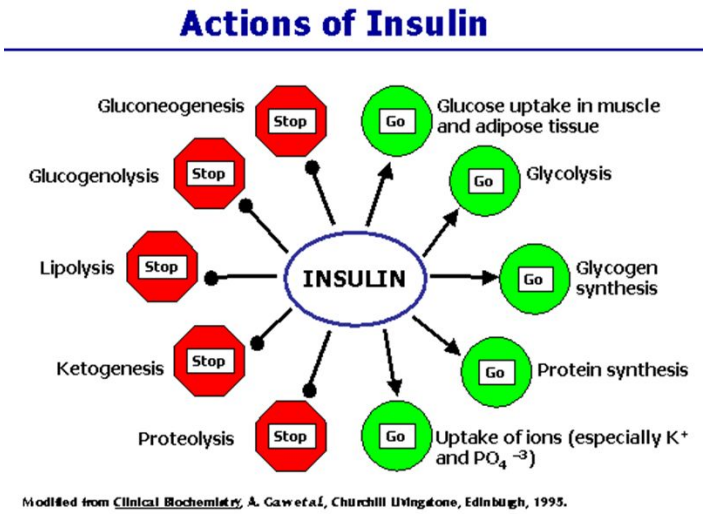
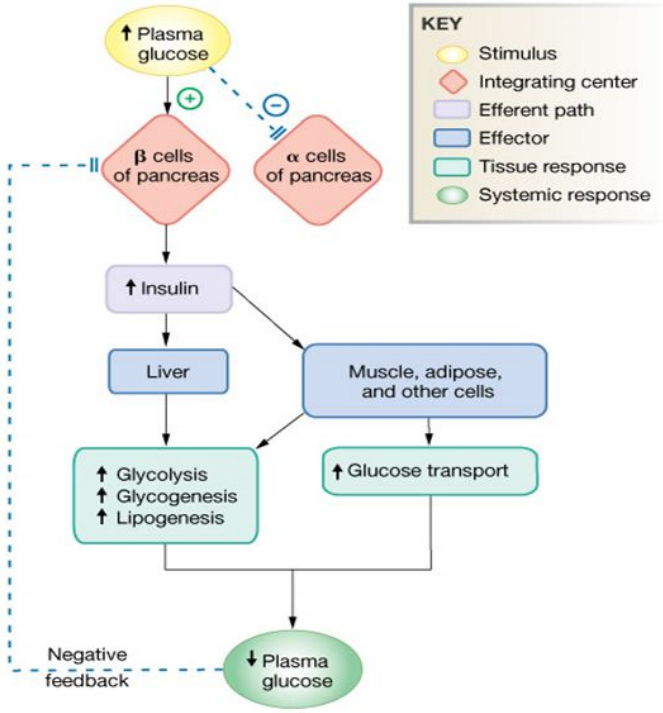
[1] The ketone bodies are an important source of energy in fasting فالانسولين يثبط تصنيعها لان اصلا الانسولين مايفرز الافي حالة زيادة الطاقه فحنا مب ناقصين طاقه.
[2] Used for triglyceride synthesis & glycolysis
[3] It is a water-soluble enzyme that hydrolyzes triglycerides in lipoproteins. It is also involved in promoting the cellular uptake of chylomicron remnants, cholesterol-rich lipoproteins, and free fatty acids.
[4] HSL is activated when the body needs to mobilize energy stores (increase free fatty acid secretion). Hormones like catecholamines and ACTH can stimulate such responses. Hence the name "hormone-sensitive lipase"
[5] the principal enzyme that causes liver glycogen to split into glucose.

Release of insulin *Boys' slides only	(There is a **continuous low basal level** of insulin release, regardless of stimulus) Insulin release occurs in two phases: 1. **Immediate:** In 3-5 minutes after acute rise in glucose levels, plasma insulin levels increase 10-fold.The immediate release probably due to release of insulin granules close to the capillaries. → Insulin levels then fall about halfway back. 2. **Delayed:** Then rise again over about 1 hour.later rise is probably due to release of preformed insulin and new synthesis

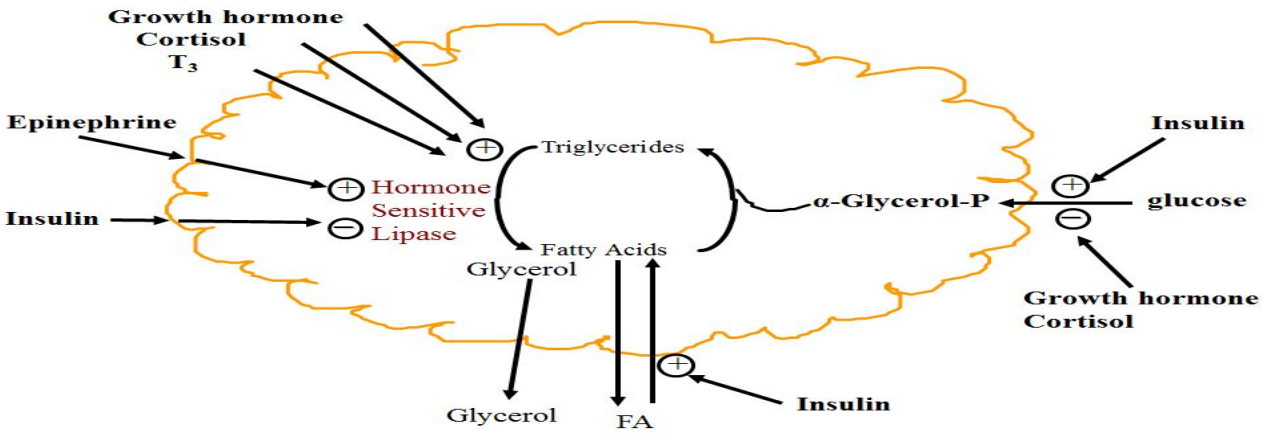


This graph shows result from infusion of glucose





Hormonal Effects on FFA Production in Adipose Tissue: *Boys' slides only



Glucagon

Definition and its origin

A 29-amino-acid polypeptide hormone that is a potent hyperglycemic agent Produced by α cells in the pancreas

Mechanism of glucagon Release *Boys' slides only

At low glucose concentrations	At High glucose concentrations
low ATP levels keep **K+ channel open,** ➔ membrane **potential** is such that **voltage dependant calcium channel is open** عكس البيتا سيلس! ركزوا ➔ **elevated intracellular calcium** levels allows **exocytosis of glucagon**	**increase ATP** levels, **closing K+ channel** ➔ membrane **depolarization** ➔ **voltage dependant Ca++ channel closes** ➔ **glucagon is not released**

Comparison of Mechanisms of Release of Insulin and Glucagon:
the calcium channels are different...

- In insulin-producing beta cells, calcium channels open in response to membrane depolarization
- In glucagon-producing alpha cells, the calcium channels close in response to membrane depolarization

Synthesis

DNA in α cells (chromosome 2) → mRNA → Preproglucagon → proglucagon → glucagon

Factors Affecting Glucagon Secretion:

Stimuli for Glucagon secretion:

- ↓ blood glucose the most imp stimulator
- ↑ **serum amino acids** (*arginine & alanine*) لاحظتو ان الامينواسيد تحفز اثنينهم الانسولين والقلوكاجون,ليش؟ عشان يبقي مستوى السكر بالدم في حالة ثبات بدون زيادة ولا نقصان..
- Stress & exercise مره مهم
- Sympathetic nervous system stimulation

Inhibitors for Glucagon secretion:

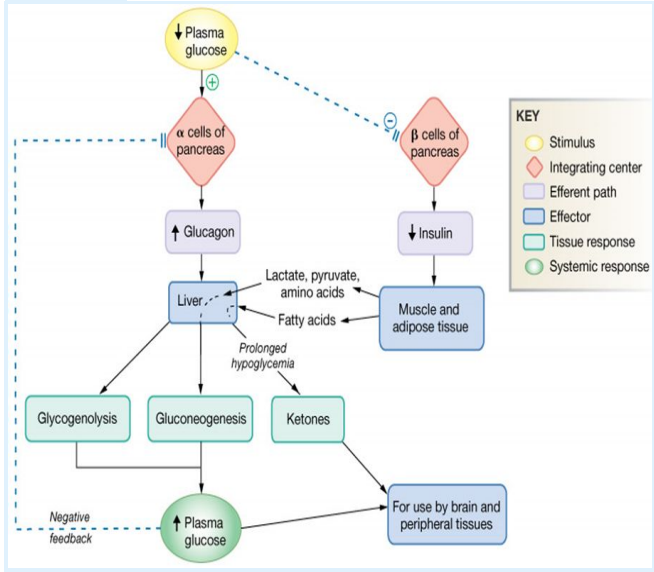
- ↑ blood glucose the most imp stimulator
- Somatostatin
- Insulin

Glucagon Actions

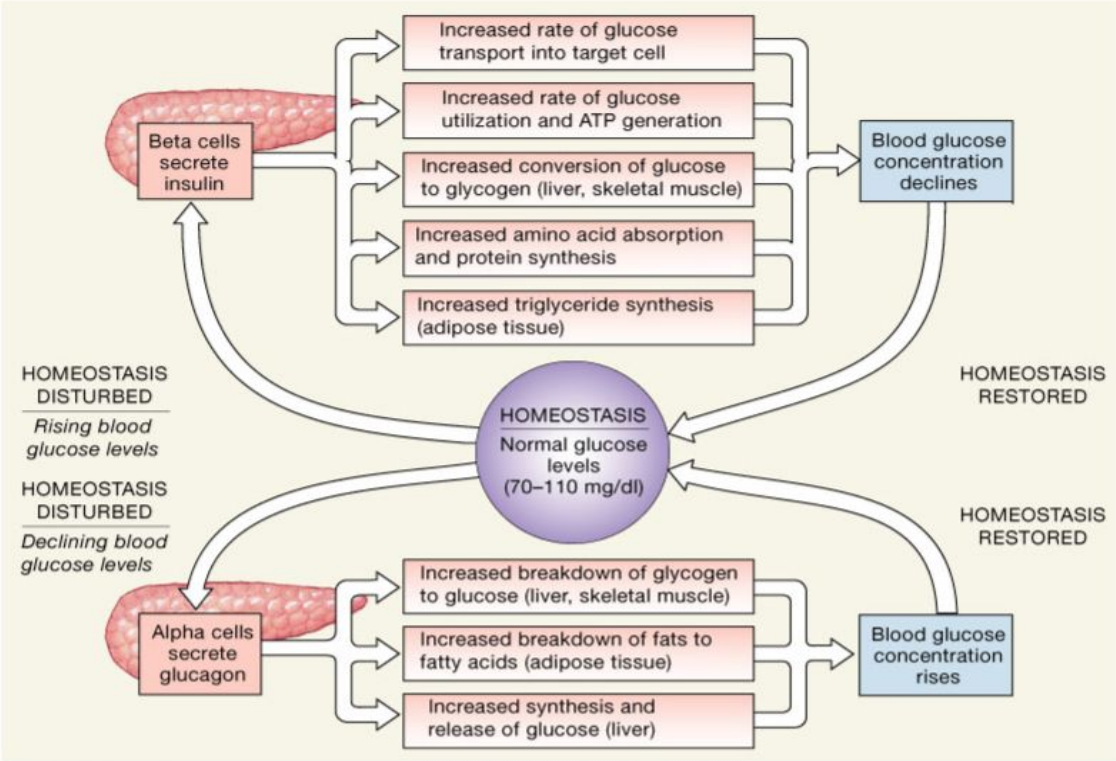
Its major target is liver: اهم شي ابيكم تعرفون تأثيره على الليفر

- Glycogenolysis
- Gluconeogenesis
- Lipid oxidation (fully to CO2 or partially → to produce keto acids "**ketone bodies**").
- Release of glucose to the blood from **liver cells**

On cells:



The Regulation of Blood Glucose Concentrations



Regulation of Blood Glucose (16 min)

Diabetes Mellitus

- It's probably the most important metabolic disease
- Affects ~2% of population: a major health problem.
- It affects every cell in the body, and affects the metabolism of:
    1. Carbohydrate
    2. Lipid
    3. Protein

Symptoms of DM:

Characterized by the **poly-triad**:

1. Polyuria (excessive urination) The high blood glucose causes more glucose to filter into the renal tubules than can be reabsorbed, and the excess glucose spills into the urine>osmotic diuresis.
2. Polydypsia (excessive thirst) This occurs partly because glucose does not diffuse easily through the pores of the cell membrane, and the increased osmotic pressure in the extracellular fluids causes osmotic transfer of water out of the cells.In addition to the direct cellular dehydrating effect of excessive glucose, the loss of glucose in the urine causes osmotic diuresis.
3. Polyphagia (excessive hunger and food consumption).why??Glut3 حنا عارفين ان البرين يعتمد على

يعني مايعتمد على الانسولين الجلوكوز يدخل دايركت له لكن في منطقة اسمها منطقة الشبع هذي المنطقة تعتمد على الانسولين لأنها تستخدم جلوت4 ففي حالة الديابيتس يعني مافي انسولين كافي هذي المنطقة ماراح يدخلها جلوكوز فهذا الشخص لن يحس بالشبع

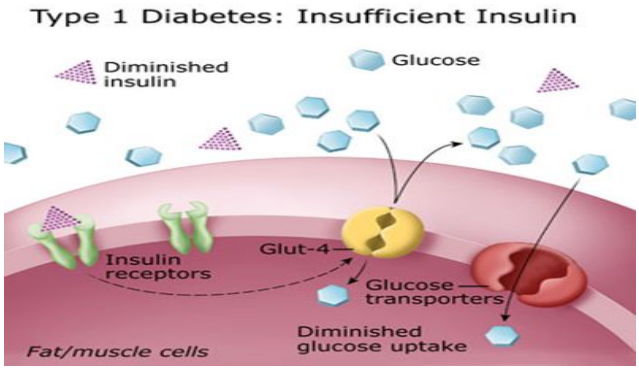
Other symptoms:

- Hyperglycemia
- Ketoacidosis (IDDM)
- Hyperlipidemia
- Muscle wasting
- Electrolyte depletion

Type 1 (insulin-dependent DM)

Affects children

Cause: inadequate insulin secretion



Resulting in Metabolic disturbances (hyperglycemia and glycosuria).

- Caused by an immune-mediated selective destruction of β cells
- β cells are destroyed while α cells are preserved:

No insulin > high glucagon > high production of glucose and ketones by liver

→ **glucose & ketones** >> osmotic diuresis

→ **keto acids** >> diabetic ketoacidosis .

ايش اخطر شي نخاف على مريض السكر منه؟؟؟COMA, طيب ايش اسباب ال COMA؟؟؟؟؟؟؟؟؟؟(ركزت عليه الدكتورة عادته ثلاث مرات)

Coma could be as result of (hyperglycemia,ketoacidosis or dehydration)

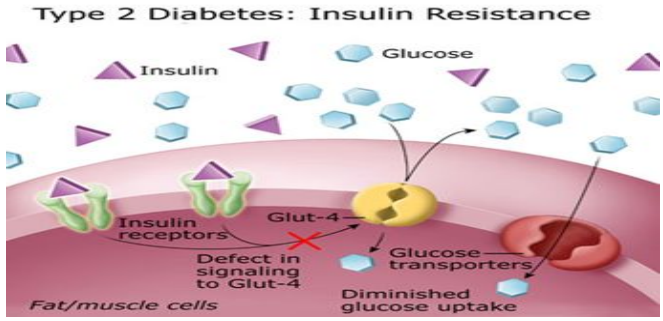
Treatment :

- Insulin injection
- In future, Type 1 diabetes might be treated with oral insulin sprays; or transplantation of b cells.
- Artificial pancreas system[6]

Type 2 (non-insulin-dependent DM)

Affects adults

Cause: defect in insulin action **(insulin resistance Is the Hallmark)**



- Type II diabetes, in contrast to type I, is associated with *increased* plasma insulin concentration *(hyperinsulinemia)*. This occurs as a compensatory response by the pancreatic beta cells for diminished sensitivity of target tissues to the metabolic effects of insulin, a condition referred to as *insulin resistance*. The decrease in insulin sensitivity impairs carbohydrate utilization and storage, raising blood glucose and stimulating a compensatory increase in insulin secretion
- Insulin resistance keeps blood glucose too high
- Chronic complications: **atherosclerosis** لان الدهون موقاعده تدخل للسل بل قاعده تترسب بالسيركيولشن**, renal failure & blindness**
- can develop into Type 1 diabetes if uncontrolled
- More common in some ethnic groups

Treatment :

- **Diet and change life style**
- **OHA** (oral hypoglycemic agents)

اضافه الى الOHA الي نعطيه لازم نعطيه اسبرين و ستاتن عشان نحمي الاوعية الدموية من ترسب الدهون فيها...

لو عندك شخص عرضة للسكري وش بتسوين؟؟ تقولين له يحسن اللايف ستال مو تبدئين على طول بتعطينه انسولين

Type 3 (gestational diabetes) سكر الحمل

*Boys' slides only

- Occurs in 2-5% of pregnancies.
- Associated with decreased insulin levels and/or insulin resistance.
- Caused by hormones that inhibit the functioning of insulin. These hormones (estrogen, cortisol, and human placental lactogen) are produced from the placenta.
- Resembles **Type 2 Diabetes**.
- Usually transient: symptoms improve following delivery.
- If untreated, causes macrosomia عملقة(high birth weight, because extra glucose delivered from the mother's blood to the fetus is stored as **fat**)

[6] ***Boys' slides:*** The artificial pancreas is not a replica organ; it is an automated insulin delivery system designed to mimic a healthy person's glucose-regulating function. The closed-loop system consists of an insulin pump, a continuous glucose monitor placed under the user's skin, and advanced control algorithm software embedded in a smartphone that provides the engineering brains, signaling how much insulin the pump should deliver to the patient based on a range of variables, including meals consumed, physical activity, sleep, stress, and metabolism.

Long Term Complications of Uncontrolled Diabetes

(MICROVASCULAR DISEASE)

Hyperglycemia damages small blood vessels:

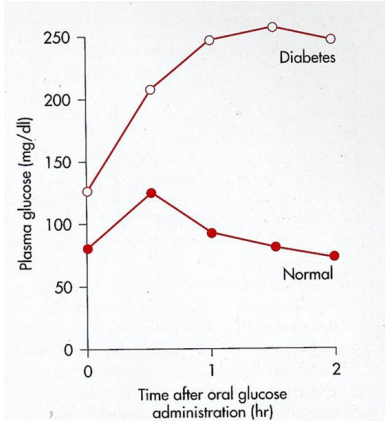
- ➔ diabetic **retinopathy** → vision loss.
- ➔ diabetic **neuropathy** → damage to nerves → most common cause of amputation in Western world.
- ➔ diabetic **nephropathy** → kidney damage → chronic renal failure.

Diagnosis

OGTT[7]: is a test that can be used to help diagnose diabetes or pre-diabetes. Both the FPG (fasting plasma glucose) and OGTT tests require that the patient fast for at least 8 hours (ideally 12 hr) prior to the test.

ترا ضروري تعرفون طريقة التيست + الهدف من التيست: يقول جبناه السنة الماضية وقليل جاوبوه، عاد ماندري :)

- **The oral glucose tolerance test (OGTT):** اهم اهم اهم تيست ينعمل اذا بتعرفين هل الشخص عنده قابليه للاصابه بالسكري او لا (لاتسوينه بالشخص المصاب بالسكري لانك تعطينه سكر فبتذبحينه)ايش نسوي اول شي تخلين الشخص يصوم اقل شي 8ساعات بعدها تاخذين منه دم وتشوفين كم سكره ثم تشربينه محلول سكر وموبه ثم تاخذين الدم منه كل ساعتين



1. FPG test
2. Blood is then taken 2 hours after drinking a special glucose solution.

- Following the oral administration of a standard dose of glucose, the plasma glucose concentration normally rises but **returns to the fasting level** within 2 hours.
- If **insulin activity is reduced**, the plasma glucose concentration takes **longer than 2 hours** to return to normal and often rises above **200 mg/dl.**

- **Measurement of urine glucose allows determination of the renal threshold for glucose.**

OGTT Condition / result	Normal values	Impaired glucose tolerance *(prediabetes)*	Diabetes
FPG	**<100 mg/dl**	= **100-125** (Impaired fasting glucose)	≥ **126 mg/dl**
2hrs PPG[8]	< **140 mg/dL**	= **140 - 199 mg/dL**	≥ **200 mg/dL**

IMPAIRED FASTING GLUCOSE Also known as pre-diabetes, this is a condition in which fasting blood glucose levels are higher than normal but not high enough to be diagnosed as type 2 diabetes. It occurs when too much glucose is released into the bloodstream from the liver overnight. The liver is mainly responsible for keeping a proper supply of glucose in the blood when we have not eaten for several hours. In impaired fasting glucose, the liver does not respond normally to the hormone insulin and this is called 'hepatic insulin resistance' ('hepatic' means 'liver'). This results in too much glucose in the blood on waking.

IMPAIRED GLUCOSE TOLERANCE This condition is also known as pre-diabetes. Blood glucose levels are higher than normal and higher than in impaired fasting glucose but still not high enough to be diagnosed as type 2 diabetes. It occurs when the insulin produced does not work properly or there isn't enough insulin released to meet the demand, or a combination of both. The result can be too much glucose in the blood throughout the day and after meals or on waking, or a combination of all three.

Glucose tolerance test 3:19

[7] The oral glucose tolerance test OGTT: is a test that can be used to help diagnose diabetes or pre-diabetes.

[8] postprandial glucose مابعد الاكل

Organs/tissue involved	Organ/tissue responses to insulin deficiency	Resulting condition of:		Signs and symptoms
		Blood	Urine	
	Decreased glucose uptake and utilization	Hyperglycemia	Glycosuria	**Polyuria** - dehydration - soft eyeballs
	Glycogenolysis		Osmotic diuresis	**Polydipsia** Fatigue
	Protein catabolism and gluconeogenesis			Weight loss **Polyphagia**
	Lipolysis and ketogenesis	Lipidemia and ketoacidosis	Ketonuria Loss of Na^+, K^+; electrolyte and acid-base imbalances	Acetone breath Hyperpnea Nausea/vomiting/ abdominal pain Cardiac irregularities Central nervous system depression; coma

 = Muscle  = Adipose tissue  = Liver

سؤال)ليش احنا دائما نقول سووا رياضة عشان تحميكم من السكري بالرغم ان الرياضة ماتحفز الانسولين؟؟؟؟؟؟؟؟؟؟؟؟؟؟؟؟؟؟؟؟؟؟؟؟؟؟؟؟؟؟؟؟؟؟؟؟؟؟؟

احنا عارفين ان العضلات تستخدمGLUT4 الي يتطلب ان الانسولين يرتبط بالرسبتر عشان يطلع من السايتوبلازم الى سطح الخليه بعدها يسمح للجلوكوز انه يدخل للخلية(ارجعو للصورة ص4 اربعه)لكن في حالة الاكسرسايز لما يصير extensive contraction يقوم الGLUT4 يطلع من السيتوبلازم الى سطح الخليه دون الحاجة الى انسولين فعلا طول يصير الجلوكوزيدخل للسل

(فالاكسرسايز هي الحال الوحيدة الي تكون فيها العضله ماتحتاج انسولين عشان يسوي expression of GLUT4)

Insulin → Increases the Glucose uptake(RESTING MUSCLE)
In contrast to the Exercising muscle it takes up the Glucose even without the action of the Insulin.

SUMMARY

pancreas	
Endocrine cells	**Exocrine cells**
Islets of langerhans produce **hormones** involved in **regulating fuel storage and use** (glucose, lipids, and protein metabolism)	**Acinar cells** produce an **enzyme**-rich juice used for **digestion**
• Beta(β) cells produce **insulin** (60-**70%**) • Alpha(α) cells produce **glucagon** (20-25%) • Delta(δ) cells produce **somatostatin (GHIH)** (5-10%) • **F** cells (or **PP** cells) produce **pancreatic polypeptide** (**5%**)	

	Insulin	Glucagon
Cell of origin	Beta cells of pancreas	Alpha cells of pancreas
Chemical nature	51 amino acid peptide	29 amino acid peptide
Biosynthesis	Typical peptide	
Transport in the circulating	Dissolved in plasma	
Half-life	5-6 minutes	4-6 min
Factor affecting release	Stimulated by: • Plasma glucose > 100 mg/dl • ↑ blood amino acids. • GI hormones (feedback reflex) • Parasympathetic Inhibited by: Sympathetic	Stimulated by: • Plasma (glucose) < 200 mg\dl, with maximum secretion below 50 mg\dl; • ↑ blood amino acids.
Target cells or tissues	**Liver, muscle, and adipose tissue primarily.** Brain, kidney, and intestine are not insulin-dependant.	**Liver** primarily.
Target receptors\ 2nd messenger	Membrane receptor with tyrosine kinase activity; pathway with insulin-receptor substrates (IRS).	G-protein coupled receptor linked to cAMP. هالمعلومة موجوده بصورة بالسلايد بس ماكتبناها الا بالسمري
Whole body or tissue action	↓ **plasma [glucose]** by: • ↑ transport into cells or • ↑ metabolic use of glucose.	↑ **plasma [glucose]** by: • gluconeogenesis and • Glycogenolysis; ↑ **lipolysis** leads to ketogenesis in liver.
Action at molecular level	↑ **glycogen synthesis** (↑ glycolysis & glycogenesis). ↑ aerobic metabolism of glucose. ↑ protein and triglycerides synthesis	Alters existing enzymes and stimulate synthesis of new enzymes.
Feedback regulation	↓ plasma [glucose]	↑ plasma [glucose] shuts off glucagon secretion.
Other informations		**Member of secretin family along with VIP , GIP and GLP-1.**هالمعلومة موجوده بصورة بالسلايد بس ماكتبناها الا بالسمري

Diabetes:

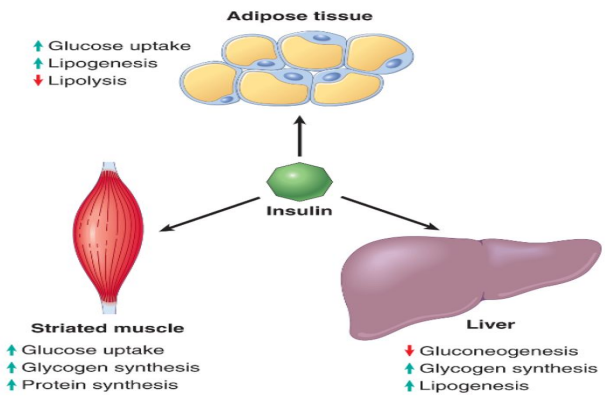
(most important metabolic disease)
affects the **cells** and **metabolism** of: carbohydrate, lipid and protein

	Type 1 (insulin-dependent DM)	Type 2 (non-insulin-dependent DM)	Type 3 (gestational diabetes)
Occur in	Children	Adults (more common in some ethnic groups)	Pregnancies
The cause	Inadequate insulin secretion, due to destruction of β cells by immune-mediated selective destruction	Defect in insulin action (insulin resistance) • Insulin resistance keeps blood glucose too high	Decreased insulin levels and/or insulin resistance due to hormones (estrogen, cortisol, human placental lactogen) that inhibit the functioning of insulin. • Resembles Type 2 Diabetes.
Symptoms	Polyuria, Polydipsia, Polyphagia		
Blood tests (OGTT)	FPG **≥ 126 mg/dl** 2hrs PPG **≥200 mg/dL**		
complications	No insulin, high glucagon (by α cells): ↑ glucose and ketones (by liver)→ **osmotic diuresis** ↑ keto acids→ **diabetic ketoacidosis**	• **Atherosclerosis**, • **renal failure** & • **Blindness** - can develop into **Type 1 diabetes** if uncontrolled	- If untreated, causes **macrosomia** *(macro= big, soma= body, = high body weight of the baby)*
Treatment	• Insulin **injection.** • In future, might be treated with oral insulin sprays; or transplantation of b cells. • Artificial pancreas system.	• **Diet** and change **life style.** • **OHA** (oral hypoglycemic agents).	• **usually transient:** symptoms improve following delivery

Long Term Complications of Uncontrolled Diabetes

(MICROVASCULAR DISEASE)

➔ **Retinopathy** → **vision loss**.
➔ **damage to nerves** → most common cause of amputation in Western world.
➔ kidney damage → chronic **renal failure**.



MCQs

1. Which type of pancreatic cells produce pancreatic polypeptides:

a. Beta (β) cells
b. Alpha (α) cells
c. Gamma (γ) cells
d. Delta (δ) cells

2. Which one is not true regarding insulin:

a. Nutrient abundant
b. Consist 2 amino acid chains linked by covalent bonds.
c. Synthesized as a pre-prohormone
d. None of above

3. Which of the intracellular receptor is the Insulin receptor :

a. Phospholipase c
b. Tyrosine kinase
c. cAMP
d. cGMP

4. Which glucose transporter is insulin sensitive:

a. GLUT1
b. GLUT2
c. GLUT3
d. GLUT4

5. Which one is not an action of insulin:

a. Decrease protein catabolism
b. Increase glucose uptake
c. Increase gluconeogenesis
d. Increase K uptake

6. At high blood glucose level glucagon …..:

a. Release elevate
b. Is not released
c. is Released in little amount
d. Is not related to blood glucose level

7. happen because of a defect in insulin action:

a. Diabetes type 1
b. Diabetes type 2
c. Diabetes type 3

8. (Rising of insulin after an hour due to release preformed insulin and new synthesis) This is called :

a. Immediate Release of insulin
b. Intermediate Release of insulin
c. Delayed Release of insulin

9. Long Term Uncontrolled Diabetes could lead to :

a. Retinopathy
b. Neuropathy
c. Nephropathy
d. All of the above

10. Somatostatin in habit :

a. Beta (β) cells
b. Alpha (α) cells
c. Delta (δ) cells
d. Both A & B

11. arginine & alanine are considered as special Stimulation factor for Glucagon secretion:

a. True (T)
b. False (F)

Answer key:

1 (C) | 2 (B) | 3 (B) | 4 (D) | 5 (C) | 6 (B) | 7 (B) | 8 (C) | 9 (D) | 10 (D) | 11 (A)

Physiology 435 team

Thanks to this amazing team!

لولوه الصغير
لينه الشهري
ربى السليمي
رزان السبتي
ريما اللحيدان
جوهرة المالكي

عمر آل سليمان
زكي الوطبان
حسن البلادي
حسن الشماسي

تم بحمد الله

لحظات شكر وتقدير لمجهود كل شخص ساهم في إخراج هذا العمل والله كنا فخورين وسعيدين بالعمل معكم ..

اقرؤوا الأسماء ثم اذكروهم بدعوة !!.. جزاهم الله خير ونفع بهم، وجعل مشاركتهم للعلم شفيعًا لهم.

لولوه الصغير
أسرار باطرفي
رغدة القاسم
حصة المزيني
ربى السليمي
مي العقيل
ريم العقيل
ريم البهلال
رزان السبتي
دانه فوزي
منيرة السلولي
ملاك اليحيى
منيرة السلمان
لينه الشهري
ريما اللحيدان
جوهرة المالكي
لميس التميمي
مروج الحربي
العنود العمير
ملاك الحامدي

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عبدالرحمن السياري
عمر الشهري
عمر العتيبي
حسن الشماسي
حسن البلادي
زكي الوطبان

وما ننسى مجهود القائدان الاكاديميان : خولة العماري ,وهشام الغفيلي ترا ماكان بس يراجع كان يضيف نوتات مهمة وشرح لكل المحاضرات تقريبا..

قادة فريق علم وظائف الأعضاء:

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