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Lipid metabolism (pages 82:104)

*Ketolysis:

-it's the oxidation of ketone bodies to produce energy يعني بكسرها عشان اخد طاقة

-Occurs in extra-hepatic tissues **only** (in mitochondria)

-Needs 2 enzymes to be occurred (الانزيمان دول مش موجودين في الكبد):

1-CoA transferase

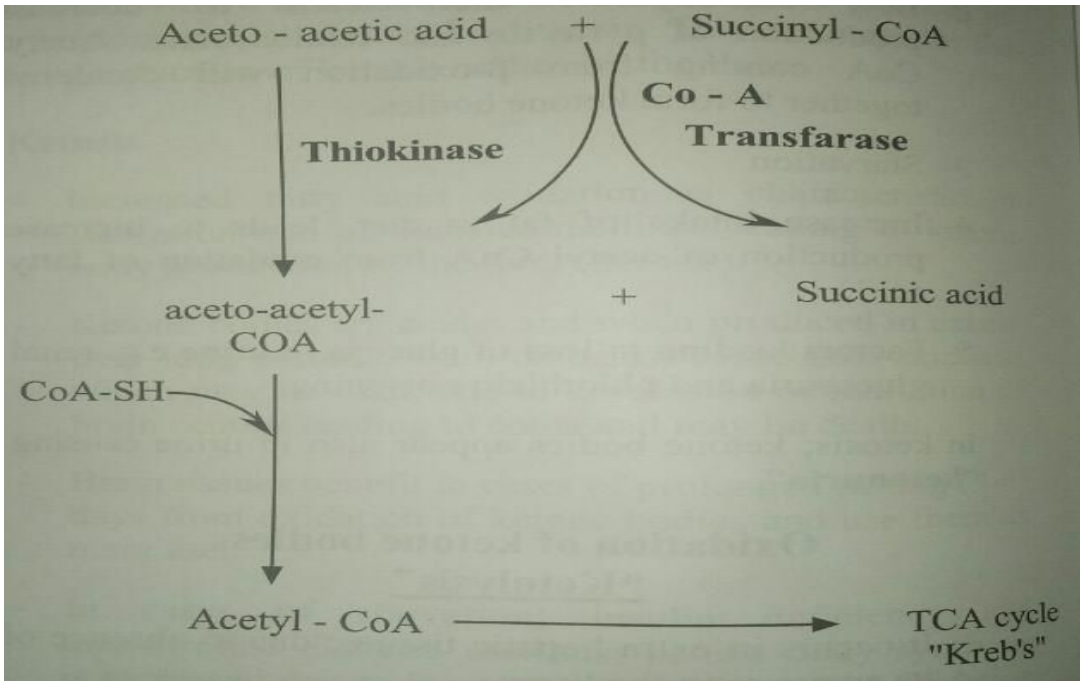
2-Thiokinase

عملية الketolysis ده بتتعمل ازاي؟

-احنا عايزين نكسر الketone bodies وندخلها في ال kreb's cycle عشان ناخد منها طاقة, ف كده لازم نحولها ل acetyl-CoA عشان ندخلها الcycle

-طب الaceto-acetate ده مافيهاش CoA enzyme!... يبقي لازم نضيف ليها CoA عن طريق اني افاعلها مع succinyl-CoA فينتقل ال CoA للـ Aceto-acetate بمساعدة ال CoA transferase وال thiokinase وتتحول ل Aceto-acetyl-CoA اللي هايتحول بعد كده ل 2 Acetyl-CoA بمساعدة ال CoA-SH (وهايتبقي الsuccinate لوحده) وبعد كده تدخل ال Kreb's cycle

يعني لازم TCA تبقى شغالة عشان اخد منها succinyl coA و عشان هيدخل فيها ال acetyl coA الي طالع، لو مش شغالة هيحصل ketosis



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*Metabolism of cholesterol:

- It's important animal steroid (not found in plant)
- More than half of cholesterol (about 700 mg/day) is synthesized inside body and the remainder is taken from **animal** food (Ex. Egg, liver, brain...)
- Dietary cholesterol (in diet) equilibrates with plasma cholesterol in days and with tissue cholesterol in weeks لما ناخد كوليستيرول في الاكل بيقعد فترة علي مايمتص في الجسم
- Normal level in blood=150-230mg%, and normal level in western countries is 5.2 mmol/L rising with age and variate between individuals
- liver and intestine synthesis about 10% of total humans' cholesterol and the rest is synthetized in all tissues
- Cholesterol synthesized in intestine is incorporated تتشق into chylomicrons
- It's synthesized by all nucleated cells in endoplasmic reticulum and cytosol
- found in all tissues and plasma as free or storage form (combined with long fatty acids chain as cholesteryl ester "Greater part")

  يعني الكولستيرول بيبقي في صورتين اما يبقي حر او مرتبط ب fatty acid لان الكولستيرول فيه OH في الكربونة التالتة اللي من عندها تقدر ترتبط ب ال fatty acid
- Cholesteryl ester in diet is hydrolyzed to cholesterol then absorbed by intestine with dietary unesterified cholesterol and lipids
- 80-90% of absorbed cholesterol is esterified with long-chain fatty acids in intestinal mucosa
- Transported in plasma by lipo-proteins (illustrated before)
- Its unit structure is acetyl-CoA
- Cholesterol and cholesteryl ester move from liver to tissues by LDL "highest portion of cholesterol found in LDL"
- Free cholesterol moves from tissues to liver by HDL (either unchanged or changed to bile acids هتتشرح قدام "يعني سواء قبل مايتحول لحمض او بعده")
- Increase of LDL may cause atherosclerosis (Ex. In Coronary artery)
- Increase of HDL isn't harmful (protective effect) عشان هو اصلا بينقله للكبد عشان يتكسر فكل ما يزيد بيحمينا من زيادة الكولسترول
- Most of cholesterol secreted by liver in VLDL then IDL then LDL which is taken up by LDL receptors, during this process cholesterol is contributed to

extrahepatic tissues then 95% of chylomicron cholesterol return back to liver as chylomicron remnants

*Synthesis of cholesterol: (5 steps)

1-Synthesis of mevalonate from Acetyl-CoA

-Two molecules of acetyl-CoA are condensed by cytosolic thiolase to form acetoacetyl-coA

-then acetoacetyl-CoA is condensed with another acetyl-CoA by HMG-CoA synthase to form HMG-CoA which is reduced to mevalonate by HMG-CoA reductase (using NADPH)

بنصنع الكوليستيرول عن طريق اننا نشبك 2 acetyl-CoA مع بعض وبعدها نحطلهم واحدة Acetyl-CoA كمان ويتكون HMG-CoA (كده بقي عندي 6 كربونات لان كلAcetyl-CoA فيها 2C ف كده 3×2=C6)

-بيدخل انزيم اسمه ال HMG-CoA reductase اللي بيحول ال HMG-CoA ل Mevalonate

HMG-CoA (3-hydroxy-3-methylglutaryl-CoA) **reductase used in cholesterol synthesis while HMG-CoA **lyase** used in ketone bodies synthesis

**Cholesterol Is synthesized extra-mitochondrial while ketone bodies are synthesized in mitochondria

2-Synthesis of isoprenoid from mevalonate

-mevalonate is phosphorylated by ATP (by 3 kinases), then active isoprenoid (isopentenyl diphosphate) is formed after decarboxylation (loss CO_2)

بنشيل من الMevalonate الCO_2فهيتحول ل Isoprenoid (كده بقي 5C عشان شيلنا واحدة دلوقتي)

3-Six isoprenoid units condensed (isomerized) to form squalene

**Squalene is linear component

4-Squalene is cyclizes into lanosterol (resembles to cholesterol)

5-Formation of cholesterol

-Lanosterol is changed into desmosterol then cholesterol

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دلوقتي احنا عايزين نصنع الكوليستيرول اللي بيتكون من C27 ف عشان نوصل للرقم ده و دلوقتي المركب اللي معانا اللي هو ال isoprenoidفيه5C ف هنجيب 6 منه ف كده يبقي عندنا C 30=6×5 وكده بقي عندنا مركب اسمه Squaleneاللي هانعمله Cyclization ويتحول ل Lanosterol وبعدها هانشيل3C منه ويتكون ال cholesterol

*Control of cholesterol synthesis (By regulation of HMG-CoA reductase):

-Inhibition of HMG-CoA reductase will decrease cholesterol level والعكس صحيح

عشان كده لو حد عنده (hypercholesteremia (increase of cholesterol بياخد ادوية تقلل (HMG-CoA reductase (cholesterol lowering drugs وبيبقي اسمها statins

-Hepatic synthesis cholesterol is inhibited by dietary cholesterol

الكوليستيرول اللي بناخده في الاكل بيعمل inhibition للكوليستيرول اللي بيتصنع في جسمنا فبيتصنع حبة قليلين عشان نحافظ علي نسبته في الجسم مايزيدش او ي ويسبب امراض عشان كده محاولات تقليل الكوليستيرول في الاكل مش لازم ينتج عنه ان نسبة الكوليستيرول في الجسم تقل

-Decrease of 100 mg in dietary cholesterol will decrease 0.13 mmol/L inside body

-HMG-CoA reductase is inhibited by:

1-mevalonate (the immediate product) and cholesterol

2-glucagon, glucocorticoid, phosphorylation (from adrenaline)

3-statins, gene regression and starvation

-while it’s stimulated by increasing of insulin and thyroid hormone

-cholesterol (or metabolite or oxygenated sterol) inhibits HMG-CoA reductase by repress يقلل its gene transcription and influence translation

-Diurnal variation occurs in both cholesterol synthesis and reductase activity

في تغييرات في تصنيع الكوليسترول بين فترة النهار و الليل

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يعني ايه gene transcription؟... يعني الgene بيعبر عن نفسه في صورة بروتين... يعني ايه برضويعني ان الgene يتنسخ ل mRNA ويحصل لل mRNA ترجمة وتتحول لبروتين

ف الكوليستيرول بقي بيثبط ال HMG-CoA reductase عن طريق انه يوقف العملية ده فيوقف شغلها

-Activity is reversely modified by phosphorylation-dephosphorylation mechanisms, some of which may be cAMP-dependent and therefore immediately responsive to glucagon

الإنزيمات بتعمل regulation عن طريق انها تعمل phosphorylation او dephosphorylation.

Insulin —> dephosphorylation —> activation of HMG-coA reductase

Glucagon —> phosphorylation —> deactivation of HMG-coA reductase

*Factors affecting cholesterol balance in tissues:

-Cell cholesterol increases due to...

1-Uptake of Lipo-protein that contain high cholesterol by receptors (Ex. LDL or scavenger التهام receptors)

2-uptake of free cholesterol to cell membrane from cholesterol-rich lipoproteins

3-Cholesterol synthesis inside cells

4-Cholesteryl esters hydrolysis by Cholesteryl esters hydrolase enzyme

-Cell cholesterol decreases due to...

1-Execretion of lipo-protein

2-Removal of cholesterol from tissues by HDL with helping of LCAT enzyme

3-Esterification by ACAT

وممكن يتصنع من الكوليستيرول حاجات تانية ف يقل زي الbile acids, steroid hormones ...

*Highly regulation of LDL receptors:

-LDL (بيتعرف علي ال apo B-100, E) receptors found on cell surface in pits coated on cytosolic side of cell membrane في غشاء الخلية من جوا by clathrin protein

-Number of LDL receptors depend on cholesterol requirement for membrane, steroid hormones and bile acids

-Types of apo B-100, E receptors:

1-high affinity LDL receptor (usually saturated)

ده بيسحب LDL كتير و موجود في الاماكن الي بتصنع steroids زي ال suprarenal cortex

2-low affinity LDL receptor is also present,in addition to scavenger pathway (not regulated)

ده الي موجود في معظم الجسم و مش بيحصلله regulation عشان هو بيسحب LDL قليل

-Defect in these receptors may cause dyslipidemia

-Steps of regulation of LDL receptor(high affinity):

1-Membrane is spannedيتمدد by glycoprotein receptor and the B-100 binding region is exposed to amino terminal end of LDL receptor الغشاء بيستعد انه يرتبط بالمستقبل

2-Then LDL receptor bind with membrane and endocytosed يعني بيتبلع لجوا

3-Then lysosomes hydrolyze apoprotein and cholesteryl ester

4-cholesterol enter the cell and receptors recycle to cell surface

لما يزيد الكوليستيرول يحصل للمستقبل ده regulation ويحصل endocytosis يعني يدخل جوا الخلية, بعدها يرتبط ب lysosome اللي هيكسر الlipo-protein اللي بعده هايكسر الlipid و هيطلع في الاخر Pre-cholesterol, و يقل الكولستيرول في الخلية

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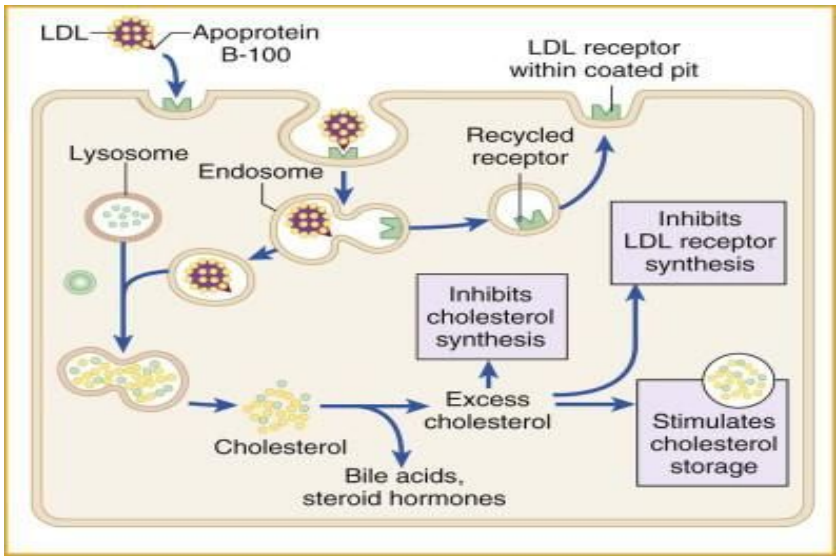

Cholesterol that entered cell **inhibits:

1-HMG-CoA synthase

2-HMG-CoA reductase

3-Cholesterol synthesis

Cholesterol that entered cell **stimulates:

1-ACAT activity

2-Down-regulates synthesis of LDL receptor بيقلل تصنيع المستقبلات فبيقل عددها على السطح

*Function of cholesterol:

1-Synthesis (precursor) of…

- bile acids and therefore bile salts
- Vitamin D_3
- Adrenal cortical hormones, Ex. Glucocorticoid, mineralocorticoid (both from suprarenal cortex) and sex hormones (from gonads)

2-Important in forming of cell membrane

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*Elimination of cholesterol التخلص منه:

-Our bodies eliminate about 1g of cholesterol per day, half of them excreted in stool (feces) in bile acids form (after digestion and absorption) and the remainder in form of cholesterol

-Bacteria in lower intestine form coprostanol (principle sterol in stool)

-Types of bile acids:

1-Primary (Ex. Cholic acid "largest amount", deoxycholic, chenodeoxycholic acid)

2-secondary

-Enterohepatic circulation:

-fat digestion products as cholesterol are absorbed in first 100 cm of small intestine

-Usually over 98-99% of the **bile acids** are **absorbed** in the terminal ileum and returned back to the liver via portal circulation زي منه بيتخلص الجسم مابدش اللي والباقي ماقولنا فوق this is called enterohepatic circulation (entero= intestine (

**Patients with hypercholesterinemia take drugs lowering enterohepatic circulation عشان يقللوا امتصاصاها في تخرج كمية اكبر بره الجسم فيقل نسبتها بالجسم

-This represent a major pathway for cholesterol elimination مع ان نسبة قليلة الي بتطلع

-About 3-5 g of bile acid is cycled every day through intestine 6-10 times, this amount is equal to the lost bile acids in stool every day and equal to that is synthesized by cholesterol. So, Pool of bile acids is constant, this is called feed back controls system

*Clinical aspects of cholesterol:

1-Atherosclerosis:

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-It's the deposition of cholesterol and cholesteryl ester from plasma lipoproteins into the artery wall

-Serum cholesterol is the main cause, but other serum lipid as triacylglycerols may play a role on it too

-Occurs due to prolonged high level of VLDL, IDL, LDL and chylomicron remnants in blood (Ex. Diabetes mellitus, lipid nephrosis, hypothyroidism and hyperlipidemia)

-susceptibility قابلية الاصابة varies widely among species and human are one of the few the disease can be induced by high diet of cholesterol

القابلية بتختلف من شخص لشخص يعني ممكن حد عنده نفس النسبة بس ما يصابش بالمرض، و في الانسان نسبة الكوليسترول في الاكل بيزود احتمال الاصابة

- Maximum ratio between LDL:HDL = 4 لو زادت عن كده بتعلي نسبة الاصابة بالتصلب

(most predictive relationship)

2-Coronary Heart disease:

-Inversely proportional with HDL concentration

كل ما بيزيد ال HDL بيقل احتمال الاصابة بالامراض

*Diet role in cholesterol level:

-Hereditary, dietary and environmental factors play important role in individual serum cholesterol level

-Replacing PUFA (polyunsaturated fatty acid) and MUFA (monounsaturated) by saturated fatty acids is the most beneficial

-Plant oil as corn and sunflower seed oil contain high PUFA while olive oil contains high MUFA while butter fat, beef fat and palm oil contain high saturated fatty acid

-Sucrose and fructose have a great effect on rising blood lipids specially triacylglycerol than carbohydrate

لانهم بيتكسروا بسرعة للوحدة البنائية acetyl-CoA

-PUFA decrease cholesterol level due to the up-regulation of LDL receptors as compared with saturated fatty acids causing increase catabolicهدم rate of LDL (The main atherogenic lipoproteinهو السبب الرئيسي للمرض)

يعني ال PUFA بتزود استهلاك ال LDL من ال Receptors فيستهلك LDL أكثر في liver فيقلل نسبة ال LDL في الدم

-Saturated fatty acids form a small VLDL particles containing high cholesterol and utilized by extrahepatic tissues at a slower rate than the large particles that may be regarded as atherogenic

ال unsaturated fatty acids تساهم في ان الVLDL اللي طالعة من ال liver انها تكون حجمها كبير و ده بيقلل من الاصابة بالامراض لان لو كانت صغيرة ال macrophages هتاكلها وهاتعمل atherosclerosis

*Effect of lifestyle on cholesterol level:

-Wrong lifestyle may cause coronary artery atherosclerosis

-Risk factors:

1-High blood pressure

2-Obesity (especially abdominal obesity)

3-Smoking

4-Male gender (females are protected due to their estrogen hormones)

5-Lack of exercise

6-Soft drinks, hard water (water containing high minerals) and alcohol

7-Factors with devotion المحبةof plasma FFA (cause increase triacylglycerol and cholesterol in the VLDL circulation), these factors include coffee drinking and emotional stress

*Primary disorders of plasma lipoprotein (Dyslipoproteinemias):

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	Name	Defect	Signs
Type 1	Familial lipoprotein lipase deficiency (Hyperlipoproteinemia)	Hypertriacylglycerolemia Due to low or abnormal LPL or low apo C-II causing inactive LPL	-slow chylomicrons and VLDL elimination -Low level of LDL and HDL -no coronary disease risk
Type 2	Familial hypercholesterolemia	Defect (increase) in LDL (Apo B-100) receptors which will increase cholesterol in blood	Atherosclerosis and coronary disease

*LPL is lipoprotein lipase

*Fatty liver:

-Definition: Accumulation of triacylglycerols (TAG) in liver

**Excessive accumulation of triacylglycerol is a pathological case, when it becomes chronic and fibrotic it will cause cirrhosis and impaired liver function and finally cause hepatic failure

-Types:

1-Type 1/ Increase of plasma free fatty acids

-Due to...

- Increase mobilization of fat from adipose tissues to blood then to liver يعني بيبقي فيه دهون كتير
- Hydrolysis of lipoprotein triacylglycerol by LPL in extrahepatic tissues
- VLDL production doesn't keep space with increasing influx and esterification of free fatty acids

يعني انتاج ال vldl مش قادر انه يعادل كمية ال fatty acids الي داخلة ال liver فهتتراكم الTAG

-This occur during...

- Starvation

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- High fat diet بيزيد الكوليستيرول عن قدرة الكبد انه يمتصه
- Not enough carbohydrate
- Uncontrolled diabetes mellitus (severe fatty liver)

بيبقي جسمهم فيه جلوكوز بس مش عارف يستخدمه

- Take high ethanol

2-Type 2/ Block in plasma lipoprotein production

-Allow accumulation of triacylglycerol

-Due to...

- Block of apolipoprotein synthesis مش قادر يعمل بروتين اصلا
- Block of lipoprotein synthesis from lipid and apolipoprotein
- Failure in saving of phospholipid that are found in lipoprotein
- Failure in secretory mechanisms

-Causes of fatty liver:

1-Excessive intake of fat and carbohydrates in diet (Type 1)

2-Increase mobilization of fat from tissue to liver (Type 1) this is due to:

A. Uncontrolled diabetes
B. Starvation
C. Decrease carbohydrate in diet

يعني زيادة الكربوهيدرات هيخليها تتحول لدهون فتزود الدهون الي رايحة للكبد، و نقصها هيخلي الجسم يكسر الدهون الي متخزنة في الانسجة عشان ينتج طاقة فهيزود الدهون الي رايحة للكبد بردو

3-Deficiency of **lipotropic factors** that cause decrease mobilization of fat from liver to adipose tissue يعني بيقلل خروج الدهون بره الكبد, so it'll decrease VLDL too

4-Liver toxic injury, Ex. CCL_4, arsenite and heavy metals as lead

5-Alcoholism ادمان الكحول (lead to hyperlipidemia and cirrhosis too)

لان الكحول بيتاكسد جوا الجسم للوحدة البنائية الacetyl-CoA

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6-Deficiency of high biological value protein (lead to decrease synthesis of β -lipoprotein) “due to not enough essential amino acids”

7-Deficiency of vitamin…

- **B_6:** convert essential fatty acids and synthesize sphingomyelin (Found in animal cell membranes and myelin sheath)
- **Pantothenic acid:** Produce CoA-SH (for β -oxidation)
- **B_{12} and folic acid:** Important in transmethylation reactions (transfer methyl group to another component, Ex. For cholic acid synthesis)

8-Antibiotics (inhibit protein synthesis)

9-Release of stress hormones

****Lipotropic factors:**

-Help in:

- mobilization of fat from liver to adipose tissues بتساعد خروج الدهون من الكبد
- Change triacyl-glycerol to phospholipid

-Examples:

1-Constituent of phospholipid: مكون من مكونات الفوسفوليبيد

- Choline: ex. Lecithin, plasmalogen and sphingomyelin
- Ethanolamine: important for choline synthesis
- Serine: ex. Phosphatidyl serine
- Essential fatty acids

2-Casein: protein in milk, rich in serine

3-Active methionine and betaine (methyl donners): important for choline synthesis

4-Vitamins (B6, B12, folic acid, pantothenic acid): important for phospholipid synthesis

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-Protection against fatty liver: نعكس الاسباب

1-Balanced diet (balance carbohydrates, fats, high biological value protein, vitamins and minerals)

2-Physical exercise

3-Avoid stress and toxins

4-Treatment of diseases (Ex. Diabetes, anemia…)

5-Take enough lipotropic factors

6- avoid alcohol

*Hormones regulated lipid metabolism (lipogenesis):

-insulin:

- It's anabolic hormone من الهرمونات اللي بتبني
- Provide glycerol, glycerol-phosphate and acetyl-CoA
- Increase lipogenesis and acyl-glycerol synthesis
- Stimulate oxidation of glucose to CO_2 so it stimulates pentose phosphate pathway which produce $NADPH+H^+$ (it's co-enzyme that is needed in reduction for fatty acid synthesis)
- Decrease blood glucose by stimulate uptake of glucose into adipose cells through GLUT 4 transporter
- Inhibit fatty acids release from adipose tissues (decrease free fatty acids and glycerol in plasma) يعني الانسولين بيقلل تكسير الدهون وخروجه خارج الكبد

**affected by rate of esterification and rate of lipolysis

- Inhibit hormone-sensitive lipase activity

**Adipose tissue is much sensitive to insulin so it's the major site of insulin action in vivo يعني النسيج الدهني هو اكتر مكان بيتم فيه تفاعلات الانسولين داخل الجسم

-Several hormones increase lipolysis (release free fatty acids from adipose tissue), Ex. Epinephrine, norepinephrine, glucagon, adrenocorticotropic (ACTH), α and

β -melanocyte stimulating (MSH), thyroid stimulating (TSH), growth hormones (GH) and vasopressin

- Many of these hormones activate hormone-sensitive lipase
- Glucocorticoid and thyroid hormones are important in lipolysis because they act in a facilitatory or permissive capacity with respect to other endocrine factors

عشان تشتغل الهرمونات ده كويس محتاجة ترتبط بمستقبل ف يزودوا عدد المستقبلات ويحسنوا ارتباطها ف تتحسن العملية كلها (يعني الهرمونات ده مش بتاثر مباشرا علي العملية لكنها بتحسن ال action of other hormones)

- Catecholamines promote lipolysis rapidly by stimulating of adenylyl cyclase (which convert ATP to cAMP by stimulating cAMP-dependent protein kinase, activates hormone-sensitive lipase), this process is similar to stimulating of glycogenolysis

*Leptin:

-Function:

1-Body weight regulatory hormones

2-Stimulate lipolysis

3-Inhibit lipogenesis

4-Act on receptors in hypothalamus

**this occur by affecting the enzyme activity in pathway for break-down and synthesis of fatty acids

-Decrease of leptin will cause: Obesity

-derived from: adipocyte hormone