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Gluconeogenesis (From 38:47)

*Definition:

It's the formation of glucose (or glycogen) from non-carbohydrate source

*Importance:

1-supply blood with glucose during carbohydrate deficiency (EX. Fasting, low carbohydrate diet, starvation or glycogen reserves

**After long fasting our body use the stored glucose (Glycogen) in liver & muscles, when glycogen is consumed too, the body makes gluconeogenesis process

2-Supply of glucose is necessary for nervous system and RBCs (erythrocytes)

*Site:

In liver (mainly) and kidney

*Sources:

1-pyruvate and lactate (Produced by muscles and RBCs)

2-glucogenic amino acids (EX. Alanine, cysteine)

3-Glycerol (Produced by adipose tissue)

4-Propionyl CoA

*Pathways of the conversion of these sources into glucose:

1-Pyruvate and lactate

All steps of glycolysis are reversal except for these three irreversible (unidirectional reaction) steps:

يعني كل خطوات تكسير الجلوكوز كان فيها السهم في الاتجاهين ماعدا التلاتة اللي جايين دول السهم في اتجاه واحد بس

Glycolysis	Gluconeogenesis (reversal glycolysis
الانزيمات اللي بتعمل تفاعلات ال irreversible	الانزيمات اللي بنحتاجها عشان نعكس عمل الانزيمات اللي في الخانة الاولي ده

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Glucokinase	Glucose-6-phosphatase بيشيل الفوسفات
Phosphofructokinase-1	Fructose-1,6-bis-phosphatase بيشيل الفوسفات
Pyruvate kinase	-Pyruvate carboxylase -phosphoenolpyruvate carboxykinase (PEPC)

**All gluconeogenesis enzymes are present in cytosol except pyruvate carboxylase which presents in mitochondria

-يعني في اخر واحد اللي هو ال pyruvate kinase مافيش انزيم واحد يقدر يتغلب عليه, او الانزيم اللي يقدر يتغلب عليه انزيم cytosolic مش mitochondrial, ف واحد من الانزيمين (اللي في الجدول) اللي هيتغلبوا عليه ده mitochondrial enzyme اللي هو ال pyruvate carboxylase, ف كده لازم يدخل ال mitochondria الاول

-ويتحول ل Oxalo-acetate ويتحول بعد كده في لفة ال citric cycle لmalic acid

-بعدها يخرج بره الmembrane لل cytosol ويتحول تاني ل Oxalo-acetate اللي هيتحول بمساعده ال PEPC ل Phosphoenol pyruvate اللي هيتحول لجلوكوز

-الخطوات تاني بالترتيب بقي كده:

1-Conversion of **pyruvate** into **oxalo-acetate** (inside mitochondria by pyruvate carboxylase)

2-Conversion of **oxalo-acetate** into **malic acid** (during citric cycle)(ده ميقدرش يطلع برا فهيتحول الاول)

3-Exist of **malic acid** into cytosol

4-Conversion of **malic acid** into **oxalo-acetate** (in cytosol)

5-Conversion of **oxalo-acetate** into **phosphoenol pyruvate** (By PEPC)

6-Conversion of **phosphoenol pyruvate** into **glucose** (By reversal of glycolysis)

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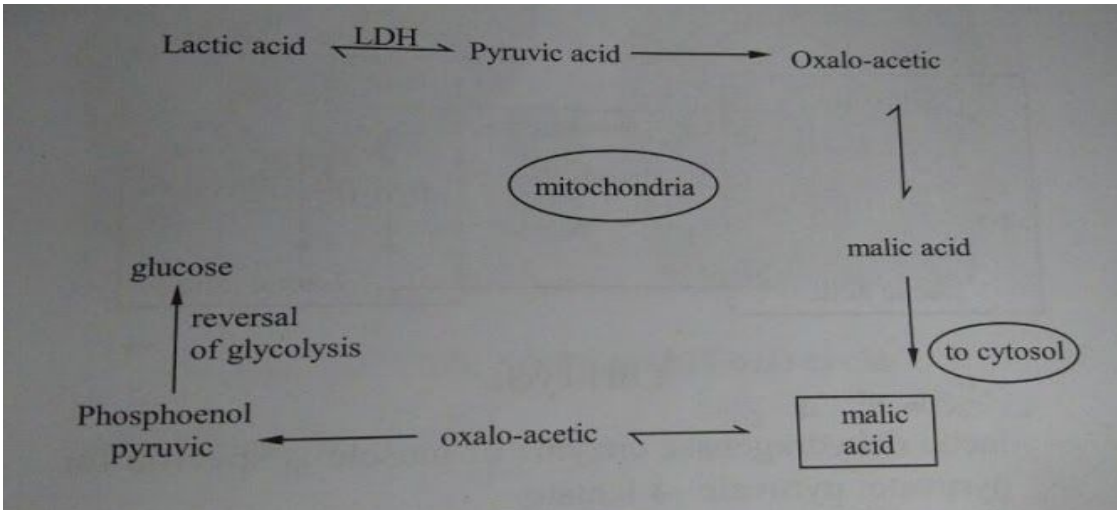

**Notes:

-Failure of gluconeogenesis is usually fatal

-Hypoglycemia (Decrease of glucose) causes brain dysfunction that leads to coma, compulsion and death

*ده بيحصل لان في خلايا ماتقدرش تاخد ال energy بتاعها غير من الجلوكوز زي lens, retina, renal medulla, RBCs

-Our tissues (especially nervous system) can't take their energy from lipid and protein without oxalo-acetate

-Glucose is important for keeping the level of inter mediates of citric acid cycle although the fatty acids are the main source of acetyl CoA in the tissues

*حتي لو انا جبت ال acetyl Co-A من الfatty acids ده مش هيغني الcitric acid cycle عن ال oxalo-acetate , لازم يشتغلوا هما الاتنين مع بعض

-Metabolism of lactic acid (Cori-cycle)

-in skeletal muscle,

Glucose is converted into lactic acid by **anerobic glycolysis**, then glucose diffuses in blood moving into liver

-in liver,

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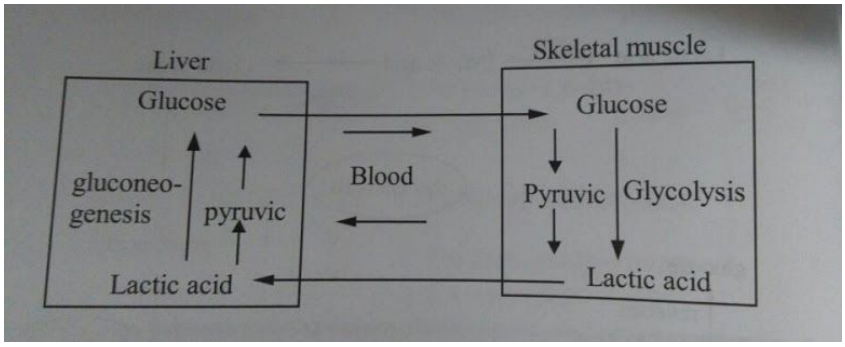
Lactic acid is converted into glucose by **gluconeogenesis**, then liver provides blood with glucose which muscle will take it again and so on...



**Notes:

-Lactic dehydrogenase enzyme (LDH) in:

1-Skeletal muscle is specific for **pyruvate** (pyruvate → lactate)

2-liver is specific for **lactate** (Lactate → pyruvate)

-**Anerobic** glycolysis of glucose produces **lactate** while **aerobic** produces **pyruvate**

2-Glucogenic amino acids:

All amino acids can give glucose except **leucine** and **lysine** which are pure ketogenic (mixed and glucogenic can give glucose)

Ex. Alanine → pyruvate (By transamination)(التفاعل ده بيمشي في الاتجاهين)

Pyruvate → Oxalo-acetate

3-Glycerol

الجليسرول ده مرتبط ب 3 fatty acids فبقدر احوله لجلوكوز عن طريق اني اعمل له:

1-Phosphorylation by glycerol-kinase in liver and kidney which will convert it into **glycerol-3-phasphate**

**Glycerol-3-phosphate is phosphate triose

2-Convert glycerol-3-phasphate into di-hydroxy-acetone phosphate by glycerol-3-phosphate-dehydrogenase

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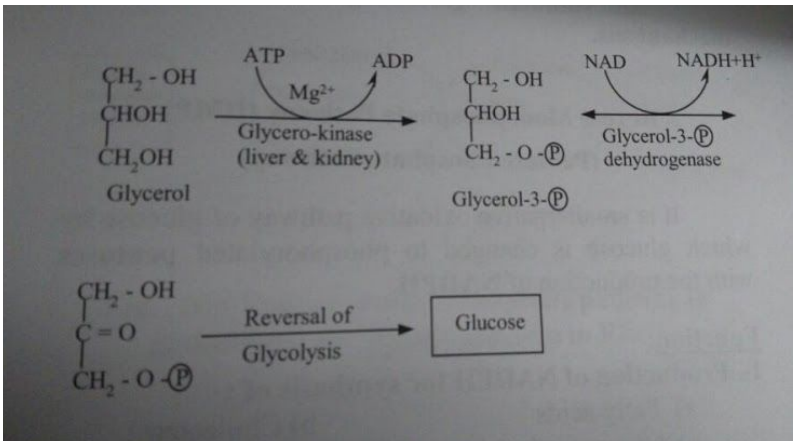
**و ده من ضمن ال intermediates اللي هايتحول بعد كده لجلوكوز



4-Propionyl CoA

-Have 3 carbon atoms

-Converted into succinyl CoA then glucose

Propionyl CoA → Succinyl CoA → Glucose

*Hormonal regulation of gluconeogenesis:

1-Insulin: inhibits gluconeogenesis by decreasing the activity of gluconeogenic enzymes لان الانسولين وظيفته يقلل الجلوكوز في الدم

2-anti-insulin: stimulate gluconeogenesis by different mechanisms (EX. Epinephrine, norepinephrine, glucagon, growth hormone, glucocorticoids as cortisone)

*Hexo monophosphate (pentose phosphate)(HMP) pathway:

-It's an alternative (minor) pathway to glucose يعني بيدخلها كمية جلوكوز قليلة

-Glucose is changed to phosphorylated pentoses with production of NADPH

-Function:

1-Prduction of NADPH by glucose-6-phosphate dehydrogenase, which:

A. synthesis fatty acids, cholesterol and adrenocortical hormones

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B. protect RBCs against free radicals and oxidations (which are toxins)

2-production of pentose EX. ribose, ribulose and xylose which synthesis nucleotides, nucleosides and nucleic acid, RNA and DNA

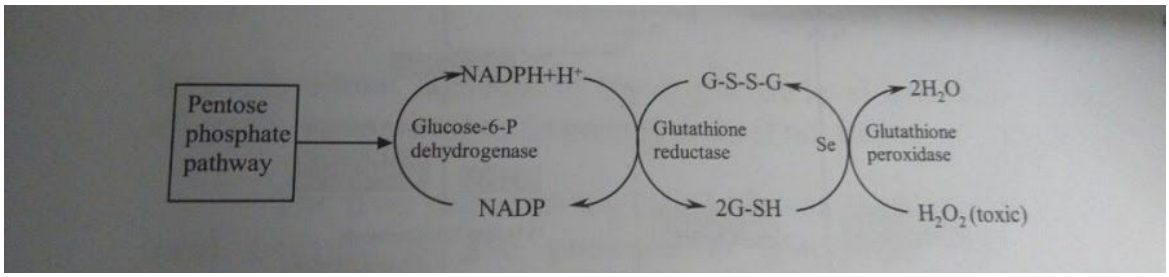
**HMP pathway doesn't produce energy

**Glucose-6-phosphate dehydrogenase is the first enzyme in HMP pathway

-Pathway:

-ال NADPH+H بيطلع بمساعده ال Glucose-6-phosphate dehydrogenase, ف لما يبقي عندي NADPH+H كافي هيساعد الGlutathione reductase انه يعمل reduction للOxidized glutathione و يحوله ل Reduced glutathione

-ال reduced glutathione بيساعد ال glutathione peroxidase انه يحول الhydrogen peroxide اللي هو (toxic (free radical ل water وكده بيحمي ال RBCs ضد الtoxins



-Disease:

Genetic deficiency of glucose-6-phosphate dehydrogenase causes hemolysis of RBCs that leads to **hemolytic anemia** or **favism** انيميا الفول

The defect appears during exposure to oxidants (free radicals), EX. Antimalarial drug, primaquine, aspirin, sulfonamides or fava beans

*Normal levels of blood glucose:

-During fasting (8-12hours fasting): 60 or 70 – 110 mg%

-During post prandial (2 hrs after eating):(<180mg%)(usually 140%)

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**لو عدي 140 ووصل اعلي من 180 mg% بتبدي الkidney ماتقدرش ت reabsorb blood glucose فابينزل جلوكوز في ال urine وده مش صحي عشان كده ال... ↓

-Renal threshold: 180mg% (=Capacity of kidney to reabsorb blood glucose)

hyperglycemia: *If **post prandial** blood glucose level increases over 180 mg%

*if **fasting** blood glucose lecel increases over 110 mg%

if **fasting level** decreases less than 60 mg%, it leads to **hypoglycemia** which will cause coma, compulsion and death

-Glucokinase helps the liver to regulate blood glucose level after eating by increasing hepatic utilization of glucose

-Insulin is secreted during hyperglycemia to decrease blood glucose level by:

1- Stimulate liver to make glycogenesis (storing glucose in liver as glycogen)

2- Stimulate glycolysis (glucose oxidation)

3- Inhibit gluconeogenesis

4- Help reuptake of glucose into extrahepatic tissues

-Glucagon is secreted during hypoglycemia to increase blood glucose level by:

1- inhibit glycogenesis and glycolysis

2- stimulate gluconeogenesis and glycogenolysis in liver عكس الانسولين

*Regulation of blood glucose:

-Liver, extrahepatic tissues and hormones keep the stable normal blood glucose level

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-Liver cells are freely permeable to glucose through **GLUT2** transporters زي البوابة المفتوحة

-Extrahepatic tissues (Except pancreatic β cells) are relativity impermeable but their glucose transporters are regulated by insulin (SO, uptake of glucose is the rate-limiting step in utilization of glucose) يعني الي بيحدد استهلاكهم للجلوكوز هي كمية الجلوكوز الي بتعدي الغشاء و تدخلهم

-Liver, brain, RBCs, renal medulla, lens and retina uptake glucose without needing for insulin (They're insulin-independent)

- **The organs responsible for regulation:**

1) **liver**
2) **Kidney**