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# Glucose metabolism

()

## Introduction

Glucose metabolism is central to mammalian cells, as the main molecule used for energy and through its derivatives to synthetize many biocompounds, from nucleic acids to lipids and glycogen (and cellulose in plants). Part of that, it is further highly regulated and supports many other functions.

So, measuring the enzymes and metabolites is pivotal to biological and medical research. This technical notice provides a scientific overview of glucose metabolism paths, and tools to make these measurements quickly, easily, and accurately, for R&D or clinical science.

## Overview of Glucose metabolism

**5 steps for Glucose**: Glucose/carbohydrate metabolism can be depicted in steps 1/2/3 in "**fed-state**", while step 4 corresponds to a "**fasting-state**".

1) Glucose **absorption** from gut to blood, and then into cells. **Go [a]**

2) **Catabolism: breakdown of energy sources**: Glycolysis; TCA Cycle(tricarboxylic acid); Fructose/Galactose metabolism; and Oxidative phosphorylation chain; glycogenolysis. **Go [b]**

3) **Storage of energy**: Glycogen Synthesis and glycogenolysis, & cholesterol synthesis. **Go [c]**

4) **Fasting state metabolism**: Gluconeogenesis[c], glycogenolysis, other Sugar metabolims, & Lipolysis[l], Protein catabolism[p]. Go **[g]**, **[d]**

5) **Side pathways**: PentosePhosphate Path (HMP shunt), Other glucose metabolism[e]
and role of glucose derivates in other functions: urea cycle, synthesis of Lipids[l], Nucleic a.[n], AA/Protein Synthesis[p]

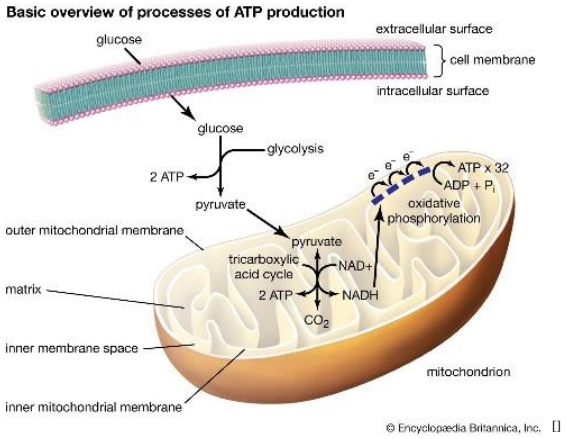
[• **Energy**: Glucose is an energy source from diet (as a nutrient or as unit of polymeric sugars), well soluble and so portable. It starts the essential process of cellular respiration to make useful energy-rich compounds: the glycolysis pathway makes from glucose ATP and pyruvate, then the TCA Cycle(rem) makes from pyruvate NADH, GTP and FADH2, and finally the oxidative phosphorylation path in mitochondria(rem) makes ATP. ATP will activate most of biochemical reactions in other metabolic processes.

Figure1: Glucose metabolism in the energy production process:
Glycolysis + TCA cycle + Oxidative Phosphorylation

Finally: Glucose + 6 $O_2$ ⟶ $CO_2$ + 6 $H_2O$ + Energy(ATP/GTP)

When oxygen is limited, pyruvate is disposed in the form of lactate and glycolysis becomes the main source for ATP production [Gatenby 2004].

Furthermore, Glucose metabolism interacts with the lipid metabolism[Parhofer 2015], with in turn represents a substantial energy supply via β-oxidation of fatty acids.




Glycolysis: 11 steps +1(Acetyl-CoA)

D-Glucose + 2ADP +2 Pi + 2 NAD+
⟶ 2 Pyruvate + 2 ATP + 2 (NADH+$H^+$) + 2 $H_2O$

TCA cycle: 10 steps / 8 enzymes

1 Ac-CoA ⟶ 2 CO2 + 3 NADH+H+ + 1 FADH2 + 1 GTP + 1 CoA.

• **Glucose derivatives and side paths**:

*Glucose, once phosphorylated to G6P during glycolysis, can enter other paths:

-**Glycogenogenesis in lung and muscles**, that is to say polymerization of G6P onto Glycogen -a storage form of glucose/2 steps). The glucose units will be returned available during fasting state via **Glycogenolysis** pathway.

-**Pentose phosphate pathway (PPP)**(rem) : 3+5 reactions/enzymes play an important role suppling sugar phosphate intermediates as key building blocks for the synthesis of nucleic acids of DNA and RNA (provides the Ribose building block -as R5P-), for the synthesis of lipids (via acCoA) and bacterial wall LPS (via S7P), for the biosynthesis of aromatic aa (via E4P>PEP) and finally for the glycolysis/TCA cycle (via F6P&Glyceraldehyde). It also generates NADPH useful for both anabolism and for the maintenance of intracellular redox homeostasis to defeat oxidative stress. PPP is so the cross-road between anabolism and *redox* balance.



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*On the other side, **gluconeogenesis** is the formation of glucose (so reversing Glycolysis) from precursors including lactate (and pyruvate), amino acids (especially alanine and glutamine), and, to a lesser extent, glycerol.

• **Glucose metabolism diseases**

Pathologies directly related to sugar metabolism include:

Diabetes mellitus | Lactose intolerance | Fructose malabsorption | Galactosemia | Glycogen storage disease.

The metabolism of glucose and its derivatives contribute to a wide range of diseases, from diabete type2 to cancers, involving deficiencies in enzymes and hormones and complexe dysregulation. More [m].

•

## Assay kits for glucose metabolism studies :

Assay kits are available to quantitate key Glucose metabolites*, to monitor chemical reaction in vitro studies, quantitate theses analytes in biological sample for clinical goals, or in cell cultures an R&D cell assays. The following is a selection including G6P, Pyruvate, and lactate, but you can find online or ask our specialists for quite any other intermediates of above glucose metabolism pathways.

The below sections presents the different glucose metabolic pathways (steps/enzymes; regulation; …), including the role of these key analytes.


*Figure:* Glucose-6-Phosphate Fluorometric Assay Kit #700300. Sensitivity: 5µM G6P. Tech Sheet (S)

| | | |
|---|---|---|
| **Glucose Uptake Cell-Based Assay Kit #600470**<br>Glucose uptake in cultured cells | **cf §-[c]** | |
| **10009582**<br>Glucose in plasma, serum, and urine | **Glucose Colorimetric Assay Kit** | |
| **600450**<br>Extracellular L-lactate in cultured cells | **Glycolysis Cell-Based Assay Kit** | |
| **700750**<br>G6P in cell lysates and tissue homogenates | **Glucose-6-Phosphate Fluorometric Assay Kit** | |
| **700300**<br>G6PDH activity in cell lysates and tissue homogenates | **Glucose-6-Phosphate Dehydrogenase Activity Assay Kit** | |
| **700510**<br>L-Lactate in cultured cells, plasma, saliva, serum, urine, and whole blood | **L-Lactate Assay Kit** | |
| **700470**<br>Pyruvate in cultured cells, plasma, saliva, serum, urine, and whole blood | **Pyruvate Assay Kit** | |
| **700480**<br>Glycogen content in tissue homogenates | **Glycogen Assay Kit** | **cf §[2]** |
| **700410**<br>Total ATP levels in a variety of sample types | **ATP Detection Assay Kit – Luminescence** | **cf§[2]** |

Other reagents are listed in next sections, by metabolic paths.

In fed state, the following processes are active: []

**Glucose uptake**

**Glycolysis**, **PentosePhosphate Path**, **TCA Cycle** and **Oxidative phosphorylation chain**

**Glycogen Synthesis**; **Fructose/Galactose catabolism**; **other Sugar metabolims**

Connexe paths: Lipid synthesis; AminoAcid synthesis; Purine/NucleicAcid synthesis

In fasting state, the following processes are active: []

**Gluconeogenesis** and **glycogenolysis**

Connexe paths: Protein catabolism; Lipolysis; Ketone body metabolism



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## [a] Glucose uptake :

Glucose enters the cell through facilitators (**GLUT** or sometimes **SGLT** proteins), and the cell needs a way to trap it there so it can't exit the cell.

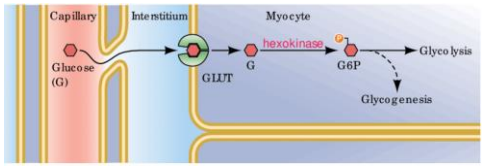



Figure from [Rose 2005]

►Ask here or search online other products:

.**GLUT** products: Proteins/Enzymes & Peptides, ELISA Kits and Antibodies

.**SGLT** products: Proteins/Enzymes & Peptides, ELISA Kits and Antibodies

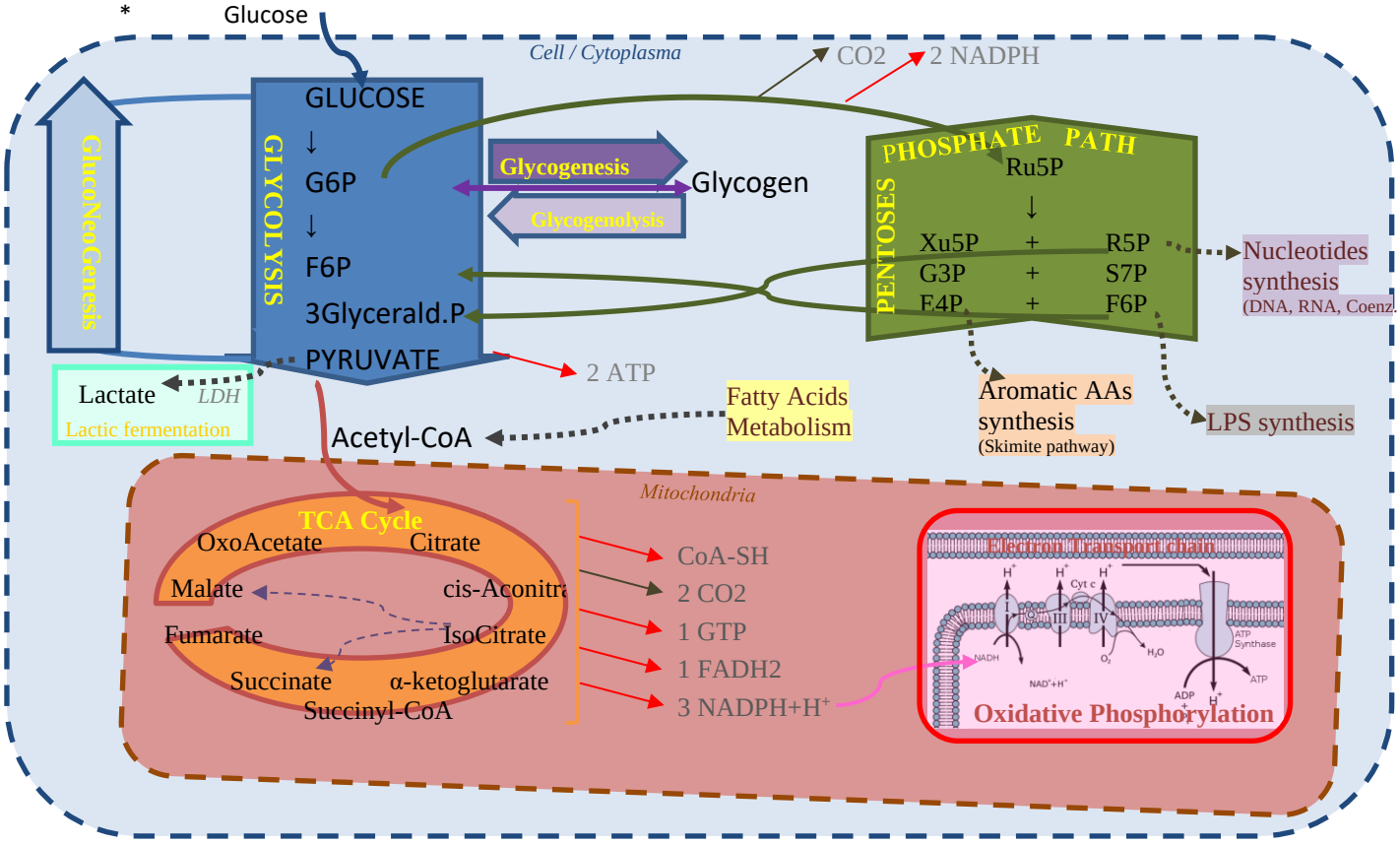
## [b] Glucose catabolism: degradation by Glycolysis, TCA Cycle, PP Path

4 key metabolic pathways are involved to degrade Glucose and make useful energy compounds:

1) **Glycolysis** followed to by the **TCA cycle** and the **OxidativePhosphorylation** in mitochondria

2) the **Pentose Phosphate path** that shunts part of the glycolysis.

*Shema* : overview of the **glucose metabolism paths** (yellow) : it include the Glycolysis, then the TCA cycle and the respiratory chain, mostly for energy production, and, more for anabolism & synthesis, the Glycogen-esis/-lysis, the GlucoNeoGenesis and the Pentoses Phosphate Path (PPP).



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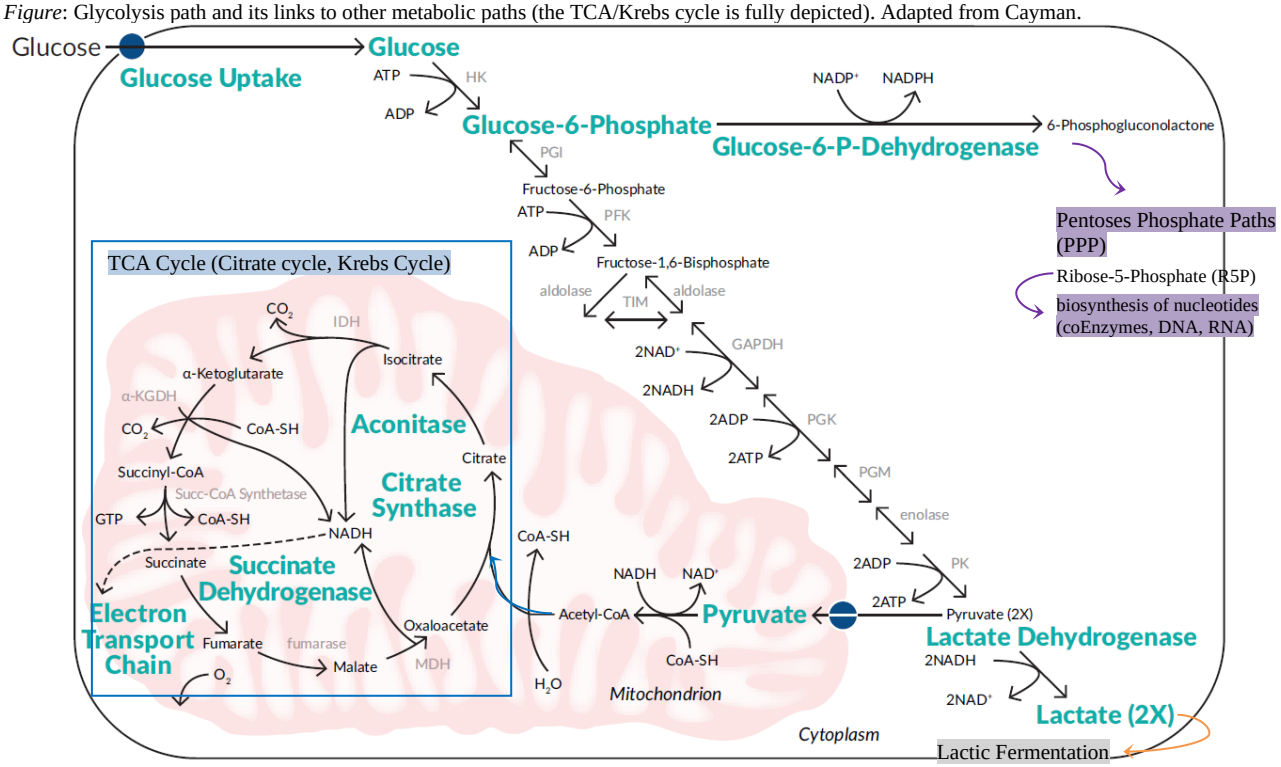
## • Glycolysis[(rem)]

The **glycolysis** path (or Embden–Meyerhof–Parnas pathway) degrades glucose to pyruvate, which can convert in Acetyl-CoA or enter the TCA cycle.

In anaerobic conditions pyruvate can be reduced to lactate[()].

Glycolysis is highly regulated, by self/retro-inhibitions (by own metabolites: G6P, F2,6P;, ATP/AMP balance) and hormones (Glucagon/Insulin).

*Figure*: Glycolysis path and its links to other metabolic paths (the TCA/Krebs cycle is fully depicted). Adapted from Cayman.




*Balance*: Glycolysis: 11 steps/10 enzymes

*(overall reaction)* D-Glucose + 2ADP +2 Pi + 2 NAD+ ⟶ 2 Pyruvate + 2 ATP + 2 (NADH+H$^+$) + 2 $H_2O$

*Regulation*: PFK-1 (Inhibited by ATP, Citrate; Activated by AMP, F2.6P) (speeded by insulin; slowed by glucagon)

Pyruvate kinase (Inhibited by ATP, Ac.CoA; Activated by AMP, F2,6P) (in liver, inhibited/slowed by Glucagon/Insulin)

Hexokinase (Inhibited by G6P)

*Relations with other paths*:

The G6P intermediate of glycolysis can enter the Glycogenesis path, or the PentosePhosphate Path, while the end-product Pyruvate conversion to Acetly-CoA links to the fatty acids metabolism.

The pyruvate can enter a lactic acid fermentation in anaerobic conditions (desH2 with ATP consumption), or in some organisms an ethanolic fermentation.

Fructose (sugar from fruits) and Lactose/galactose (from milk) must undergo certain extra steps in order to enter the glycolysis pathway. See §[d].



HexoKinase (HK)
Glucose-6-phosphate isomerase (PGI)
Phosphofructokinase-1 (PFK)
Fructose-bisphosphate aldolase
Triose-phosphate isomérase (TIM
Glycéraldéhyde-3-phosphate deshydrogenase (GAPDH)
Phosphoglycérate kinase (PGK
Phosphoglycérate mutase (PGM)
Énolase (phosphopyruvate hydratase)
Pyruvate kinase (PK)



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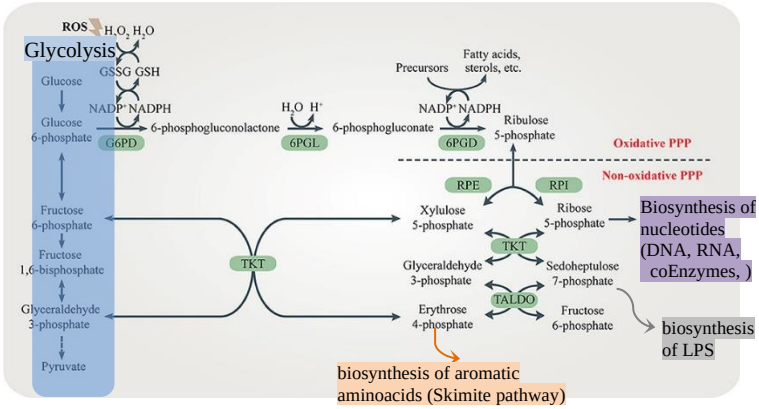
## • Pentose Phosphate Path (PPP) (rem)

The **pentose phosphate path (PPP)** (or Warburg-Dickens-Horecker path) converts G6P to several pentoses that undergo rearrangement, up to 3-GlyceroPhosphate that can go back to the end of glycolysis.

*Figure*: pentose phosphate path (PPP) and its links to other metabolic paths. Adapted from [Ge 2020]




Modified from [Ge 2020] (fig.1) *

The 1st phase is oxidative (and produces NADPH), while not the next steps that generates useful sugar building blocks:

- for the glycolysis (via Fru6P, 3GP. Non-glucosidic glycosides can be degraded up to acetyl-CoA),
- for the biosynthesis of aromatic aminoacids (via *E4P*),
- for the synthesis of nucleotides (via the ribose *R5P*),
- for the synthesis of bacterial wall LPS (via *S7P*).

*Balance*:

*(overall reaction)* Glucose 6-phosphate + 2 $NADP^+$ + $H_2O$ ⟶ ribulose 5-phosphate + 2 NADPH + 2 $H^+$ + $CO_2$

*Relations with other paths*:

The PPP provides sugar phosphate intermediates as key building blocks for the synthesis of nucleic acids of DNA and RNA (provides the Ribose-as R5P- building block), for the synthesis of lipids (via acCoA) and bacterial wall LPS (via S7P), and also for the biosynthesis of aromatic aa (via E4P>PEP) and finally for the glycolysis/TCA cycle (via F6P&Glyceraldehyde). It also generates NADPH useful for both anabolism and for the maintenance of intracellular redox homeostasis to defeat oxidative stress. PPP is so the cross-road between anabolism and *redox* balance.

The PPP intermediate R5P (phosphorylated Ribose) feeds the biosynthesis of nucleic acids.
From E4P (Erythrose-4P), the shikimate pathway makes PEP (phosphenopyruvate), the precursor of phenylalanine and then of other aromatic aminoacids (Try, Tyr).+



glucose-6-phosphate deshydrogenase (G6PD)
6-phosphogluconolactonase (6PGL)
6-phosphogluconate deshydrogenase (6PGD)
ribose-5-phosphate isomérase (RPI)
phosphopentose épimérase (RPE)
transcétolase (TKT)
transaldolase (TALDO)

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## • TCA Cycle (rem)

Then the acetyl-CoA enters the **TCA cycle** (tricarboxylic cycle cycle, or citric cycle, or Szent-György cycle, or Krebs cycle) to produce energy under a form used by other cell metabolism paths: ATP, GTP and NADPH.

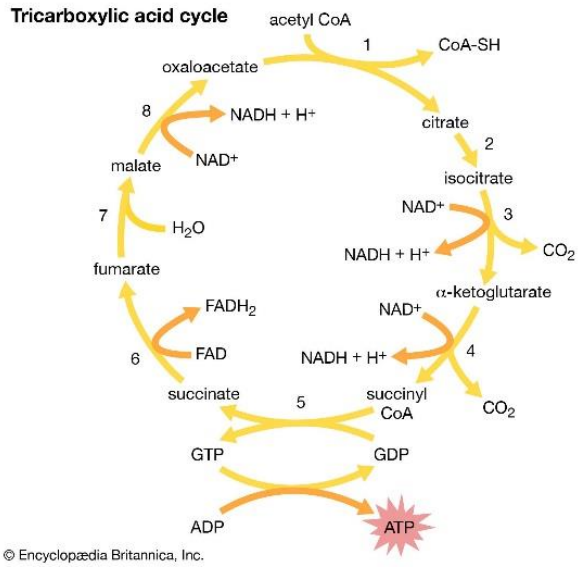


*Figure*: TCA Cycle. Adapted from Britannics Encyclopedia

The TCA cycle in linked downstream to amino-acid biosynthesis (via the *2OxoGlutarate, Fumarate, OxaloAcetate*), to the metabolism of lipids (via the *Citrate*, *Malate/Glyoxylate*) and to the metabolism/biosynthesis of purine nucleotides (via the *Fumarate*): see below figure.

*Balance*: TCA cycle: 10steps/8enzymes

*(overall reaction)* 1 Acetyl-CoA ⟶ 2 CO2 + 3 NADH+H$^+$(2.5 ATP per) + 1 $FADH_2$ (1.5 ATP per) + 1 GTP + 1 CoA.

*Regulation*: The TCA cycle is controlled through the enzymes that make the first 2 molecules of NADH: the isocitrate dehydrogenase and α-ketoglutarate dehydrogenase. The metabolites (NADH, Ac-CoA, ATP, ADP) inhibit or activate them allosterically, so the cycle is regulated by feedback inhibition. Finally, the cycle activity depends mainly on the ATP and NADH levels. $Ca^{2+}$ level is also involved.

+

*Relations to other paths*:

The TCA cycle is linked to the biosynthesis of aminoacids, purines, and fatty acids:

•The TCA cycle is linked to following metabolic up- or down-stream paths through 6 of its metabolites:

1) 2OxoGlutarate => biosynthesis of aminoacids (Lys, NH4/Glu, As, Ile, Leu, Tyr, Val, Orn, Arg, His, pSer, and Gln (nitrogen assimilation)
=> biosynthesis/metabolism of purines (NAD)
2) Fumarate => biosynthesis/metabolism of nucleotides (AMP)
<= degradation of Argino-Succinate & AminoAcid generation
3) Malate <= synthesis of malate with Ac.CoA+Glyoxylate
4) OxaloAcetate (+Glu) <=> Aa biosynthesis of Asp (+ 2OG)
5) Citrate (+CoA+ATP) => Mevalonate pathway, et Fatty Acid elongation (Lipids metabolism)
6) Acetyl-CoenzymeA <=> link to the fatty acid metabolism (see next paragraph)

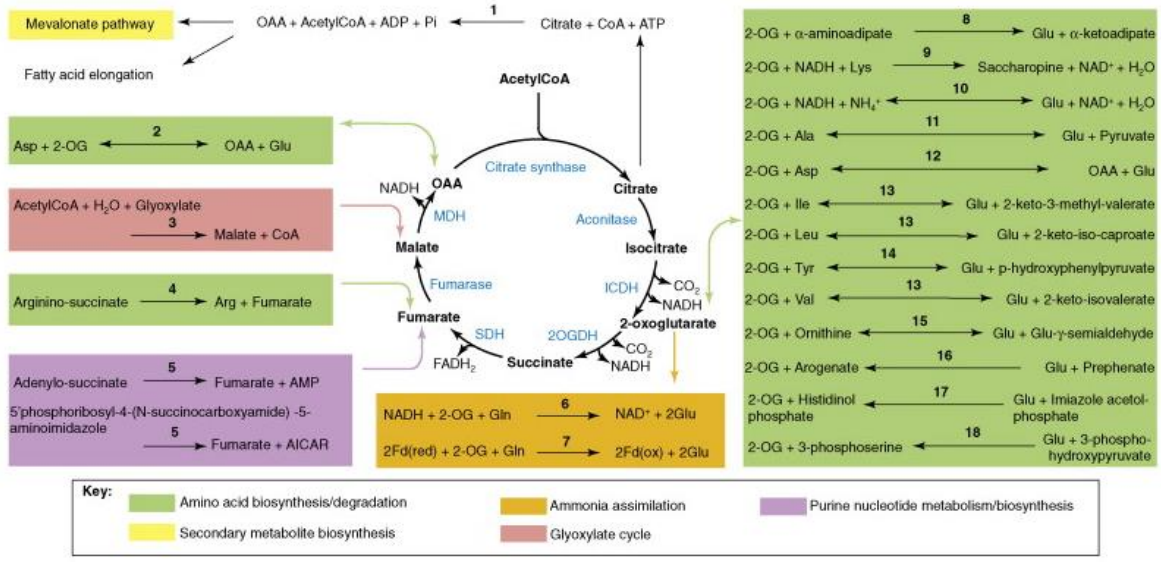


*Figure*: TCA Cycle and it's link to to other metabolic paths. From [Sweetlove 2010]

Not just a circle: flux modes in the plant TCA cycle | Lee J. Sweetlove et al. | Trends in Plant Sciences, 15, Issue 8, P462-470, August 01, 2010



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•The TCA Cycle supplies carbon chain to the FattyAcids metabolism via its Acetyl-CoA feed stock converted to Pyruvate, and can reciprocally be fed in Acetyl-CoA substrate (in place of the glycolysis)

Remarks:

The degradation of glucose is linked to more oxidative metabolism reactions (not covered by this article): see products in page Oxidative metabolism and Mitochondria, including probes and assay kits for ROS/NO/Catalase/Malondialdehyde/GSH/SOD, LDH; POD, MPO, … The page Diagnostic lists tests for clinical biomedical chemistry: Alcohol Dehydrogenase (ADH); β-Hydroxybutyrate (Ketone Body); Total Antioxidant Status (TAS); Total Oxidant Status (TOS), Oxidases (Glycolate , MAO, DAO, PPO, XOD); Bilirubin (TBIL; DBIL) ; VitamineE;…



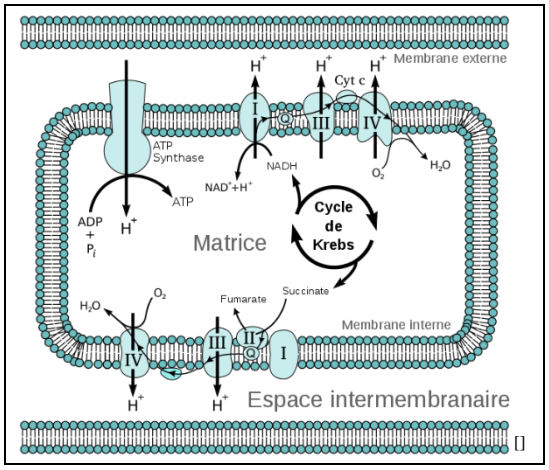
| | | | |
|---|---|---|---|
| Citrate synthetase | α-cétoglutarate deshydrogenase | Succinyl-CoA synthetase | Malate deshydrogenase (MDH) |
| Aconitase | 2-oxo-glutarate deshydrogenase (2OGDH) | Succinate deshydrogenase (SDH) | |
| Isocitrate deshydrogenase (ICDH | | Fumarase | |

## • Oxydative Phosphorylation chain

The **Oxydative Phosphorylation chain** converts in the mitochondria the energy-rich compounds produced by the TCA cycle to a trans-membranar gradient of protons, that will active the ATP synthase (by the proton influx) to make ATP from ADP and Pi.

In eukaryotes, 4 membranar complexes and several cofactors (including complexes I, III, and IV to excrete H+; complex II, CoEnz.Q10, Cytochromes a/b/c, FAD) participate to the OxPhos process, transporting electrons with a declining oxidative potential up to the final reaction $O2 + 2H^+ + 2e^-$ -> H2O . The ATP synthetase is also membranar.

Rem: the reactions are more/less different in the procaryotes et archeans.




*Balance*: *(overall reaction in eukaryotes)*

$$1\ \text{Acetyl-CoA} \longrightarrow 2\ CO_2 + 3\ \text{NADH+H}^+ + 1\ FADH_2 + 1\ \text{GTP} + 1\ \text{CoA}.$$

+

*Regulation*: Oxidative phosphorylation is regulated primarily by the energy needs of a cell, and therefore the ratio of ADP to ATP: the final stage of cellular respiration where the combined action of the electron transport chain and chemiosmotic coupling result in ATP production.+



ATP Synthetase

+

## [r] regulation of glucose

The overall metabolism of glucose is regulated by several retro-feed back and specific mechanisms described in above sections (Glycolysis; PPP, TCA cycle). Finally nucleotide energy-rich couples regulate the energy metabolism, and is fed by different upstream processes from msec to minutes times (see section 'Cell energy control through ATP/ADP/AMP, and NAD(P)/NAD(P)H ATP/ADP/AMP and NAD(P)/NAD(P)H levels').

A remarkable regulation relies on 2 key hormones, which production depends on the amount of nutrients currently available. Insulin and glucagon released from the pancreas are the primary hormones involved in maintaining a steady level of glucose in the blood.

[Rose 2005] Skeletal Muscle Glucose Uptake During Exercise: How is it Regulated? | Adam John Rose et Erik A Richter | Physiology, Sep.2005

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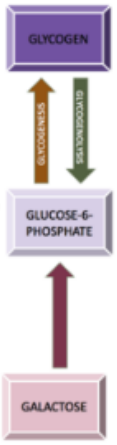
►Ask here or search online more products:

.**Insulin** products: Proteins/Enzymes & Peptides, ELISA Kits and Antibodies, standards
.**Glucagon** products: Proteins/Enzymes & Peptides, ELISA Kits and Antibodies, standards

## [c] Glycogenesis and Glycogenolysis (glucose storage & mobilization)

Both animals and plants temporarily convert the energy released by the metabolism of nutrients, in particular glucose, in the form of high-energy molecules, such as ATP, for use in various cellular processes.
For longer terms, the energy of glucose is stored as a polymer, glycogen, in liver and in muscles, and could be mobilized back to ATP during fasting, to fuel cell energy and biosynthesis.

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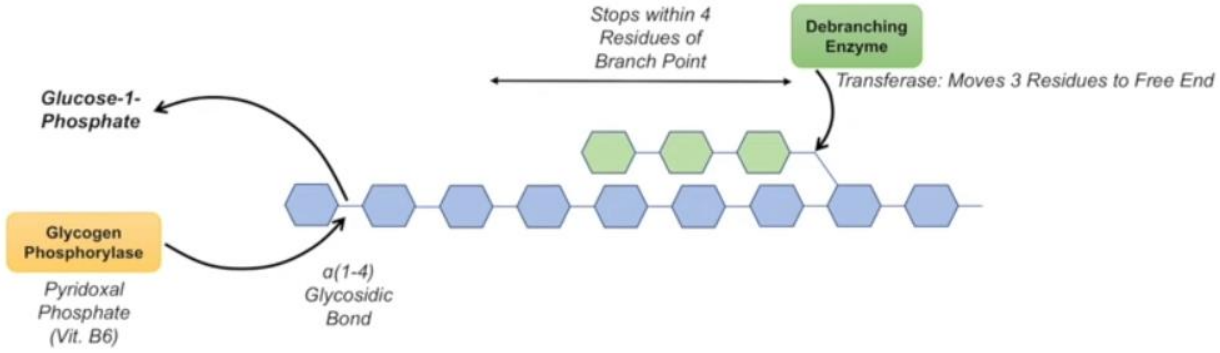
•**glycogenesynthesis:** The glucose storage compounds is synthetized from Glucose (phosphorylated by the first step of Glycolysis) as follows:
G6P ⟶ G1P, (+UTP) ⟶ UDP-Glc (+P1), (+Glycogen$^{(n)}$) ⟶ UDP Glycogen$^{(n+1)}$ *Details below*

•During fasting state, the **glycogenolysis** breaks down glycogen back to glucose units:
Glycogen-UDP (+ATP, Glycogen hydrolase) ⟶ G1P ⟶ G6P ⟶ Glucose *Details below*
*Balance*: 3 ATP generated per Glucose (only 2ATP per non-glycogen glucose)
Finally, the benefits for Glycogen are a) in muscles: the rapidity of energy delivery in anaerobic conditions but with limited storage capacity and size (low ATP/mass), and, b) in liver, to maintain the blood glucose levels. Higher needs are covered by lipids (see [l]).

Both paths occur in the cytoplasm.

* Remarkable assay product :
**700480** **Glycogen Assay Kit**
Glycogen content in tissue homogenates

• **glycogenolysis** : Glycogen is lyzed by 3 enzymes:

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-the **Glycogen Phosphorylase** cleaves α(1-4) linked Glucose residues and releases G1P (that will be isomerized to G6P for further uses). It needs vitamin B6$^{(pyridoxalPhosphate)}$. However, it stops within 4 residues from branch point. So a **debranching enzyme** is required:
-a Glucosidase hydrolyses the α(1-6) branching bonds and release free Glucose (not G1P)
-a transferase moves 3 Glucose residues to free end.

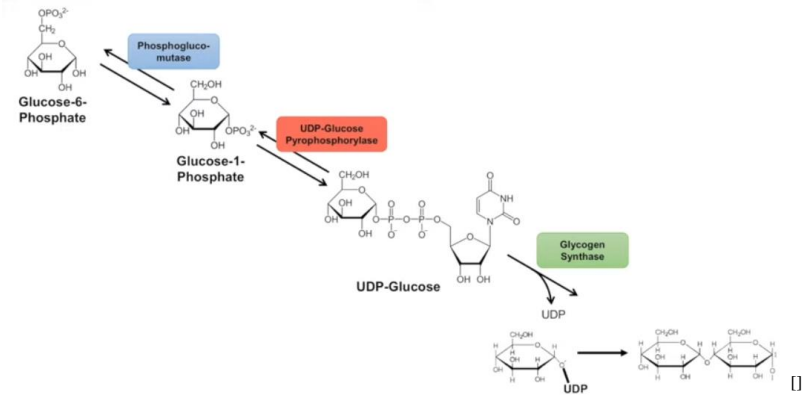
• **glycogenesis** : The Glycogen is synthetized by 3 key enzymes:

-Upstream activation of Glucose to G6P (shared with Glycolysis)

-Isomerization (converts G6P to G1P) by **PhosphoGlucoMutase**(PGM)

-Activation to UDP-Glucose by **UDP-Glucose Pyrophosphorylase**.

-Addition of G1P to a Glycogen chain by the **Glycogen Synthetase**, using UDP energy. This enzyme is expressed upon insulin activation of protein phosphatase, and inhibited by a protein kinaseA activated par Glucagon and epinephrine.



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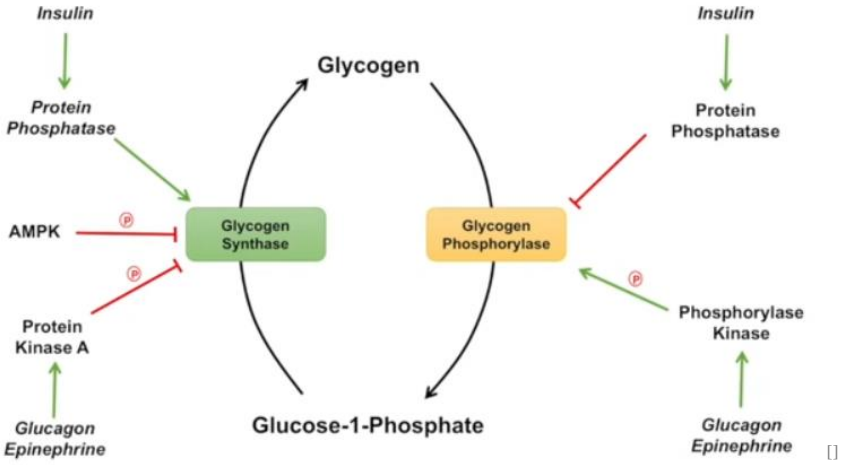
Note: Glucose from diet has to be phosphorylated (this occurs in the 1st stop of glycolysis, to G6P followed by a isomerization to G1P by a GlucoMutase).

• **Regulation:**

It is noteworthy that Glycogen synthase and Glycogen phosphorylase are respectively down- and up-expressed upon insulin activation of a protein phosphatase, and up- and down-inhibited by Glucagon and epinephrine (through a phosphorylase kinase and a a protein kinaseA respectively).



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In liver, the G.Phosphorylase is also inhibited by ATP, G6P and Glucose. Only liver (and a little in kidneys) have a G6-Phosphatase to convert actively G6P to Glucose.

The situation is similar in skeletal muscle is that the G.Synthetase is stimulated by $Ca^{2+}$ and by AMP (instead of Glucose inhibition), so 2 markers of muscle active contraction. Also the conversion of G6P to Glucose is quite inoperant so G6P is degraded by glycolysis.

## [d] Gluconeogenesis : Glucose synthesis

In case the glucose is lacking in diet, to keep a stable glycemia (~1g/L of Glucose in blood), some cell can synthesize glucose from non glycosidic materials: 3 ways:

-Lactate/Pyruvates (for muscle in activity; and bacteria without mitochondria)

-Glucoforming aminoacids, typically Alanine.

-Glycerol (by adipociary lipolysis).

The **gluconeogenesis** is the formation of glucose from precursors including lactate (and pyruvate), amino acids (especially alanine and glutamine), and, to a lesser extent, glycerol. It so reverses Glycolysis (in red in figure4).

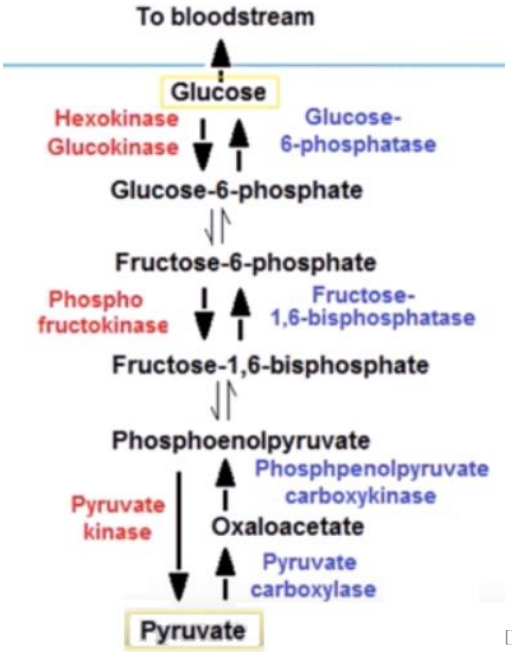


*Figure* : 4 enzymes differ in NeoGlucoSynthesis (in blue) compared with Glycolysis (in red)

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* Remarkable assay products :

**L-Lactate Assay Kit #700510**
L-Lactate in cultured cells, plasma, saliva, serum, urine, and whole blood

**Pyruvate Assay Kit #700470**
Pyruvate in cultured cells, plasma, saliva, serum, urine, and whole blood

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Proteins; Peptides; Enzymes; ELISA Kits; Antibodies; Standards(e.g. #70048); Diagnostics

Glycogen: Proteins/Enzymes & Peptides, ELISA Kits and Antibodies, standards

Pyruvate carboxylase

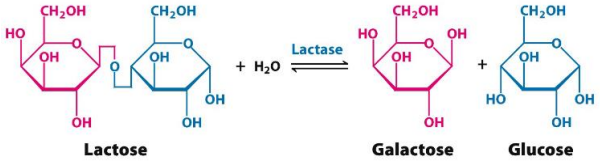
phosphoenolpyruvate carboxykinase

Fructose 1.6-bisphosphatase

Glucose 6-phosphatase.

## [f] Gluconeogenesis: Fructose, Lactose/galactose, Mannitol, DEHU (sugars metabolism)

Fructose (sugar from fruits) and Lactose/galactose (from milk) must undergo certain extra steps in order to enter the glycolysis pathway.




•**Lactose** :

Lactose, which is converted to galactose and glucose by the lactase enzyme, is the primary carbohydrate for developing mammals, and in humans it constitutes 40 percent of the energy consumed during the nursing period.

Why lactose evolved as the source unique carbohydrate of milk is unclear, especially since most individuals can meet their galactose need by biosynthesis from glucose. Evolutionary reasons may include:

-presence and specific functions of galactose in glyco-proteins, complex polysaccharides, and lipids, particularly in nervous tissue

-organoleptic and physical properties of galactose

-simultaneous occurrence of calcium and lactose in milk

•**Fructose** : several paths:

Ingested fructose is directly converted to plasma triglyceride (<1%), most is converted to Glucose in liver and lactate. Glucose and lactate are then used normally as energy to fuel cells all over the body.

-Metabolism of Fructose in Muscle (anaerobic Glycolysis, with large amounts of Hexokinase) or Adipose tissue:

α-D-Fructose =====> α-D-Fructose-6-P

(Hexokinase, +ATP) └-> to Glycolysis

-Metabolism of Fructose in Liver:

α-D-Fructose =====> GAP

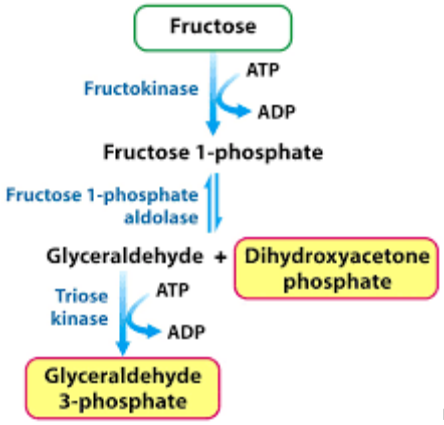
α-D-Fructose =====> DHA ⇔ GAP

└-> to Glycolysis

(Glucose ⟶ Pyruvate x2)

Fructose is metabolized almost completely in the liver in humans, where it is directed toward replenishment of liver glycogen and triglyceride synthesis. It even appears that fructose is a better substrate for glycogen synthesis than glucose and so glycogen replenishment takes place first, then triglyceride formation.

*Figure*: Fructose metabolism (liver)

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The fructose-bisphosphate aldolase plays a key role in both glycolysis and Gluconeogenesis : the isoenzyme B(liver-type) cleaves 1,6-bp-Fructose into GAP and DHAP as well as the fructose 1-p into glyceraldehyde and DHAP. The isoenzymes A and C prefer F 1,6bp.

•**Galactose** :

Galactose is a sugar found in Red Seaweeds (Glucose also)

Galactose can be activated into Galactose-phosphate by a Galactokinase and ATP consumption. G1P will then be converted to Glucose-1P in a cycle involving a transferase and an epimerase[].

α-D-Galactose =====> α-D-Glucose-6-P

(kinase, +ATP) └-> to Glycolysis

Galactose can be converted into Glucose-6-phosphate by several enzymatic reactions **(Leloir pathway)**[Lim 2014] to enter the Glycolysis pathway.

•**Mannitol** :

Mannitol contains about 60 percent fewer calories than sugar and is half as sweet. This support its use in transformed foods, despite excessive amounts can cause gastrointestinal discomfort[].
Mannitol occurs naturally in fresh mushrooms, brown algae (DEHU also), tree bark and most fruits and vegetables.

Mannitol is converted into Fructose-6-phosphate (not in S.cerevisiae).

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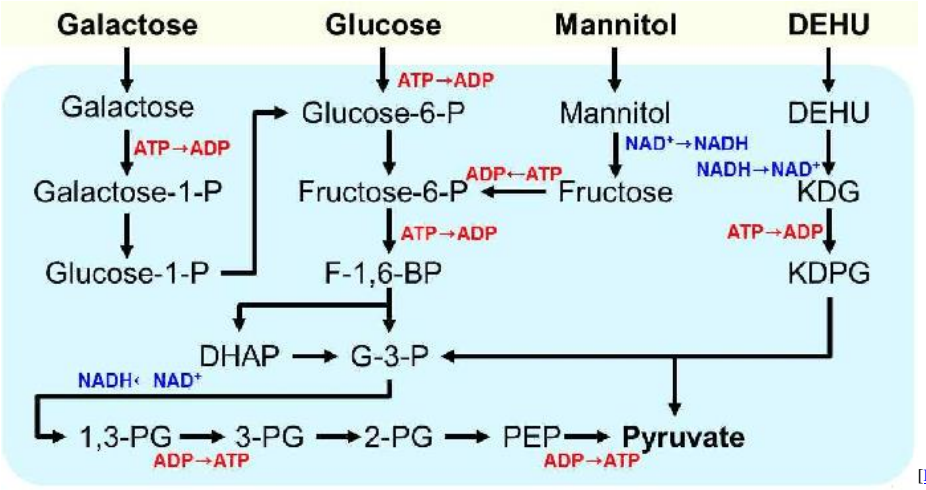

[Lim 2014]

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| Standards | |
| Antibodies(): | Fructose /Lactose )/Pyruvate /Galactose Antibodies |
| ELISA Kits(): | Fructose/Lactose /Pyruvate /Galactose ELISA kits |
| Diagnostics(): | Fructose /Lactose/Pyruvate /Galactose assay/test/dosage (colorimetric) |

## [m] Glucose metabolism diseases & pathologies

It is clear that glucose and its derivatives contribute to a wide range of diseases, from diabete type2 to cancers[Alfarouk 2020], but also biotechnology, bacterial and parasite infections, neurons, and stem cell potency. Pathologies directly related to sugar metabolism include:

Diabetes mellitus | Lactose intolerance | Fructose malabsorption | Galactosemia | Glycogen storage disease.

Understanding the pathologic processes and developing drugs require reliable monitoring of key glycosides concentration and activities of enzymes. Some have been linked to deficiencies in enzymes or particular paths with identified biomarkers, but often there are more complex dysregulations involving imbalance of [ATP]/[ADP] × [Pi] or [NADPH]/[NADP+]. The research opens new therapeutic axis like D-β-hydroxybutyrate and ketones as an alternative energy fuel in some pathologies, and diagnosis in others (large quantities of ketone bodies (75% is βHB, then acetoacetate (AcAc) and acetone) are found in the blood in case of diabetes, alcohol or salicylate poisoning, hormone deficiency, childhood hypoglycemia).

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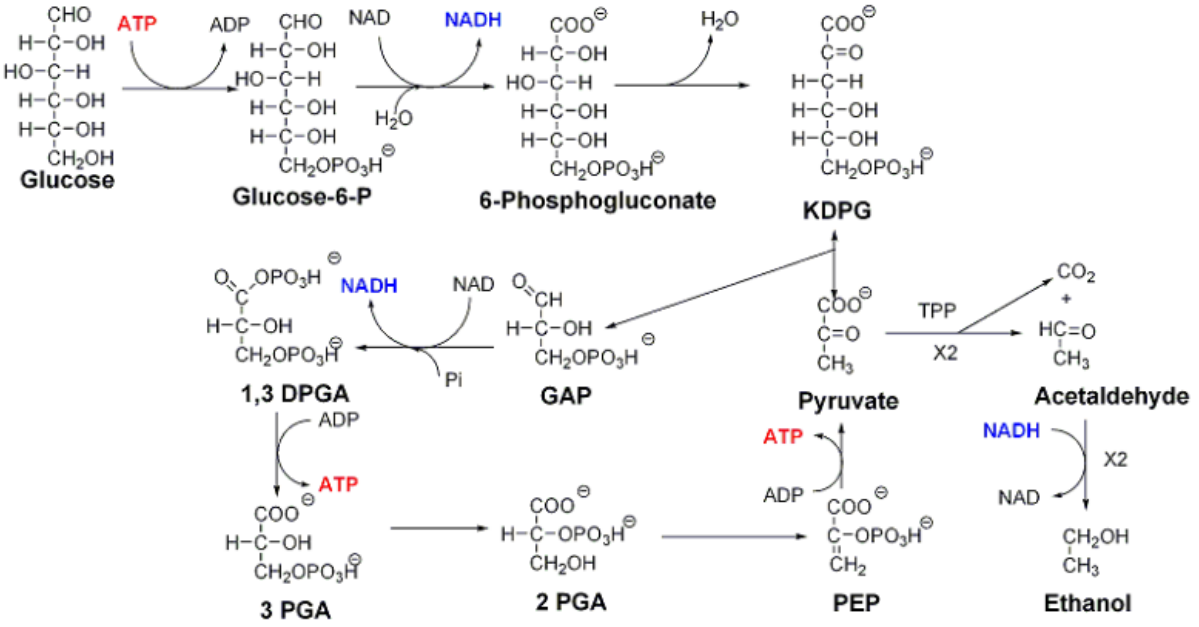
## [e] other processes : Entner Doudoroff pathway

The **Entner Doudoroff pathway** begins with hexokinase producing Glucose-6P, but produces only one ATP per glucose. This pathway prevails in anaerobes such as *Pseudomonas*, as they do not have a Phosphofructokinase.

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## [l] connected processes: Lipid metabolism - synthesis and Lipolysis (link to glucose metabolism)

The lipid metabolism is connected to the Glucose metabolism, notably through the building block acetyl-CoA produced the end of Glycolysis(see), or via the PPP(see).

The LipoPolySaccharide of bacterial wall also use a metabolite from the PPP metabolism (via E4P).

*



## [n] connected processes: Purine/NucleicAcid synthesis

The metabolism of nucleic acid and other ribose- or purine-based compounds (cofactors; nucleotides) is connected to the Glucose metabolism, notably through metabolites of the PentosePhosphate Path(PPP)(see).

-The phosphorylated Ribose (R5P) is a major building block for nucleotides and thus nucleic acids.

-The energy in the couples [NAD+]/[NADH], [NADP+]/[NADPH], [acetyl CoA]/[CoA], and [ATP]/[ADP]x[Pi], regulates the energy metabolism. This drives a great control of whole metabolism, which is widely unobserved because the energy in these coenzyme pools cannot be determined from the concentration of the coenzyme couples. This control operates through a high number of enzyme/reactions involved in cytoplasm (up 1300) and in mitochondria (up 180) [Veech 2019].

Schema: numbers of enzyme-linked reactions in which the controlling nucleotide couples are reactants and products.

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## Nucleic acid biosynthesis

The synthesis of nucleic acids occurs in the cytoplasm of notably liver cells, according one path for pyrimidine-based nucleotides (C, T, U), and on path for purine-based nucleotides (A, G), before the (oxy or desoxy)Ribose-5-P sugar (coming from the PPPath) is covalently coupled to make the nucleoside and further phosphorylations (1-3).

The purine heterocycle is synthetized mainly from the glucide metabolism.

The pyrimidine heterocycle includes atoms from the glucide metabolism (via the formate) by also from aminoacids metabolism (Gly, Glu, Asp), from ammoniac and from CO2! . Shema from wiki.

## Nucleotidic coenzymes

**•ATP / cell energy control**

The nucleotide coenzyme ATP is the primary currency of cellular energy transfer.

**•NAD/NADP : Nicotinamide nucleotide coenzymes.**

The nicotinamide nucleotide coenzymes (syn) are involved as proton and electron carriers in a wide variety of oxidation and reduction reactions.

[Bender 2003] The oxidized coenzymes have a formal positive charge, and are represented as $NAD^+$ and $NADP^+$, while the reduced forms, carrying two electrons and one proton (and associated with an additional proton) are represented as NADH and NADPH (or $NADPH+H^+$).

In general, $NAD^+$ is involved as an electron acceptor in energy-yielding metabolism, being oxidized by the mitochondrial electron transport chain, while the major coenzyme for reductive synthetic reactions is NADPH. An exception here is the pentose phosphate pathway (hexose monophosphate shunt), which reduces $NADP^+$ to NADPH, and is the principal metabolic source of reductant for fatty acid synthesis.

### Cell energy control through ATP/ADP/AMP and NAD(P)/NAD(P)H levels

The ratio [ATP]/[ADP] × [Pi] is a often use as a good indicator of the energy state, through its change or stability. It is however affected by simultaneously hundreds of enzymes with different dynamics, integrating very quick variations and more lasting ones through NAD(P)/NAD(P)H level and other upstream players.

•**ATP** utilization goes from about 0.01 µmol ATP/g/s to approximately 5 µmol ATP/g/s while the available ATP pool (approximately 7 µmol ATP/g) would last about 1 s. So other enzymes respond: see §-cell energy control through ATP and NADP

•**creatine kinase** taps into the reservoir of creatine phosphate to offer next 3–5 s of sustained ATP concentration.

Creatine-P + ADP ⇌ Creatine + ATP

However, ADP accumulation is limited by adenylate kinase: ADP + ADP ⇌ ATP + AMP

accumulation of AMP itself is limited by AMP deaminase: AMP + H2O → IMP + NH3

•The depolymerization of glucose from **glycogen** followed by glucose oxidation to lactate provides another 30 s of sustained [ATP]/[ADP] × [$P_i$] ratio.

/overall reaction:/ $(glucose)_n + 3\ ADP + 3\ Pi \rightarrow (glucose)_{n-1} + 3\ ATP + 2$ lactic acid

•Muscles consume **fatty acids** for energy in addition to glucose, preserving some glucose for the brain. As the blood–brain barrier blocks the majority of fatty acids from entering the brain, this require an alternative energy fuel in brain:

•**D-β-hydroxybutyrate** represents an alternative fuel useful for longer periods, notably in heart muscle and in the brain. βHB entries in cell then in the mitochondrion matrix (co-transported with H+) where it is deshydrogenized to 2 acCoA (SCOT, ACAT enzymes), then oxidized by the TCA cycle, producing ATP. The citrate to α-Ketoglutarate sequence is shunt hen glucose is low, but occurs in cytoplasm with NADPH production to balance redox potential. Schema from [Veech 2019, fig.3].

This makes D-β-hydroxybutyrate a singularly unique metabolite with potential to treat disease. Similarly, ketone bodies also increases the acetyl-CoA and similarly, even better, can overcome limitations in energy metabolism, as can be induced by insulin resistance suspected in several diseases (e.g. in the hippocampus with Alzheimer; dementia; Parkinson): βHB or ketones can compensate a lack of glucose and insulin, to restore CoA and NADH. Further to this path, cytoplasmic NADPH can stimulate the production of Tyrosine (with high dihydrobiopterin ($BH_2$) ratio to tetrahydrobiopterin ($BH_4$)), hence then L-DOPA. This explains why administration of βHB or ketones in diet improved Parkinson treatment (decreased dopamine production by dopaminergic neurons in the substantia nigra of the brain).
Also the free [NADPH]/[$NADP^+$] couple (restored by βHB and/or Ketones) controls the redox state of secondary redox couples linked to ROS and RNS detoxification.

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## [p] connected processes: catabolism of proteins (link to glucose metabolism):

() The glucose metabolism pathways can make and use carbon chains that are clived for/from aminoacids.
Examples:

-The Glu and Gln aa degradation products enter the TCA cycle as α-cetoglutarate and so can form sugars via the L-malate (neoglucogenesis).

-The Leu, Ile, Lys, Phe, Try and Tyr aa can supply Acetyl-CoA that will be oxidized to produce energy for cell.

-Some aa in some condition can form ketones in liver that will be eliminated through urine or the respiration.

()Dans le processus de dégradation des protéines, les chaînes polypeptidiques sont clivées par des peptidases en les acides aminés qui les constituent. Leur chaîne carbonée peut alors:

- entrer dans le cycle de Krebs — comme c'est par exemple le cas du glutamate et de la glutamine qui entrent sous forme d'α-cétoglutarate — ce qui présente un effet anaplérotique — on parle d'acides aminés glucoformateurs car ils peuvent être orientés vers la néoglucogenèse via le L-malate ;

- être convertie en acétyl-CoA pour être oxydée et produire de l'énergie, comme c'est le cas de la leucine, de l'isoleucine, de la lysine, de la phénylalanine, du tryptophane et de la tyrosine ;

- être convertie en corps cétoniques, susceptibles d'être ou bien oxydés par d'autres tissus que le foie où ils sont produits, ou bien excrétés par voie urinaire ou par la respiration — on parle d'acides aminés cétoformateurs.

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#Glucose; #Metabolism; #Assay; #Lactate; #Glycolysis; #Krebs ; #Glycogen; #ATP; #NADH; #Pentose; Phosphorylation; Deshydrogenase ; #Epimerase ; #Fructose ; #Galactose ; #lactose ; #Mannitol ; #Cayman

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