

Metabolism Enzymes

The Citric Acid Cycle

| Enzyme | Enzyme Structure | Substrate | Reaction | Inhibited by | Activated by | Notes |
|-------------------------------|--|-----------------|--|---|--|--|
| Citrate Synthase | – | Acetyl CoA | Acetyl CoA → Citrate | High [ATP] High [citrate]- product inhibition High [succinyl CoA] | High [ADP] Oxaloacetate | Citrate inhibits phosphofructokinase (glycolysis) Irreversible reaction |
| Aconitase | Fe-S protein | Citrate | Citrate → isocitrate <i>Isomerization- 3° alcohol to 2°</i> | Fluoroacetate (rat poison) | – | Reversible reaction |
| Isocitrate Dehydrogenase | – | Isocitrate | Isocitrate → α-ketoglutarate <i>Oxidative Decarboxylation- loss of CO₂ + reduction of NAD⁺ → NADH¹</i> | NADH ATP | High [Ca ²⁺]- <i>calcium signifies that a muscle cell is contracting, which requires energy.</i> ADP | Irreversible reaction |
| α-ketoglutarate Dehydrogenase | An aggregate of 3 enzymes: E1: Decarboxylase <i>TPP deficiency- α-keto acids accumulate in the blood</i> E2: Transacylase E3: dehydrogenase | α-ketoglutarate | α-ketoglutarate → succinyl CoA <i>Oxidative Decarboxylation- loss of CO₂ + reduction of NAD⁺ → NADH²</i> | Succinyl CoA- product inhibition NADH GTP Arsenite– trivalent As forms a stable complex with SH of lipoic acid <i>Neurological disturbances, death.</i> | High [Ca ²⁺] | Irreversible reaction TLCFN (coenzymes) TPP- decarboxylase Lipoic acid + CoA-transacylase FAD + NADH-dehydrogenases |

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|---|--|--------------|--|----------|---|--|
| Succinate Thiokinase <i>Succinyl CoA Synthase</i> (Reverse rxn) | – | Succinyl CoA | Succinyl CoA + GDP → Succinate + GTP <i>Cleaves thioester bond, which results in substrate-level phosphorylation.</i> | – | – | Reversible reaction <i>Nucleoside diphosphate kinase rxn converts GTP → ATP.</i> |
| Succinate Dehydrogenase | Coenzyme: FAD <i>FAD is reduced instead of NADH because the reducing power of succinate isn't sufficient for NAD⁺ reduction.</i> | Succinate | Succinate + FAD → FADH ₂ + Fumarate <i>Oxidizes succinate H₂ lost → double bond</i> | Malonate | – | Reversible reaction The only TCA cycle enzyme that's embedded in the inner mitochondrial membrane. Functions as Complex II in ETC. |
| Fumarase | – | Fumarate | Fumarate → Malate <i>Hydration- breaks double bond</i> | – | – | Reversible reaction |
| Malate Dehydrogenase | – | Malate | Malate + NAD ⁺ → NADH ³ + Oxaloacetate <i>Oxidation of malate– 2° alcohol → ketone</i> | – | – | Reversible reaction Positive delta G value, however, the largely negative delta G value of the citrate synthase rxn allows this rxn to proceed. |

Oxidative Phosphorylation

| Enzyme | Enzyme Structure | Electron Source | Transports Electrons To | Specific Inhibitor | Notes |
|--|---|--|---|---|---|
| Complex I | Flavoprotein 7 Fe-S centers (at least 2 different types) > than 25 polypeptide chains FMN is tightly bound Binds NADH & CoQ | NADH → NAD ⁺ <i>Hydride</i> | Coenzyme Q <i>Ubiquinone</i> | Rotenone (pesticide/insecticide) or amytal (sedative) <i>No transfer of electrons from Fe-S to coenzyme Q</i> | 4 protons transported across the IMM |
| Complex II <i>Succinate Dehydrogenase</i> | Flavoprotein Fe-S centers | FADH ₂ → FAD <i>Hydrogen atoms</i> | Coenzyme Q <i>Ubiquinone</i> | | Doesn't fully penetrate the IMM → no H ⁺ transported |
| Complex III <i>Cytochrome bc1</i> | Hemoprotein- <i>hemes b_H, b_L, c₁</i> Fe-S centers 11 subunits including 2 cyt. subunits | Coenzyme Q | Cytochrome C <i>Present on the outer leaflet of the IMM.</i> | Antimycin A (antibiotic) <i>Blocks transfer of e⁻ complex III cyt. C to the mobile e⁻ carrier cyt. C</i> | 4 protons transported across the IMM |
| Complex IV <i>Cytochrome a + a₃ Cytochrome oxidase</i> | Fe-Cu 2 copper sites Contains oxygen binding sites. | Cytochrome C | Oxygen <i>Final electron acceptor</i> | Azide (N ³⁻), cyanide (CN ⁻), amygdalin, and carbon monoxide (CO) | 2 protons transported across the IMM. Reduction of oxygen to H ₂ O. O ₂ must accept 4 electrons for Partial reduction results in ROS formation. Much lower K _m for O ₂ than myoglobin & hemoglobin. |
| Complex V <i>ATP Synthase</i> | 2 domains: F ^o & F ₁ F ^o : transport of protons F ₁ : enzymatic domain, synthesizes ATP from ADP + Pi | – | – | Oligomycin (antibiotic) <i>Prevents the influx of H⁺ through ATP synthase.</i> | Responsible for the synthesis of ATP. Protons flow down their concentration gradient, inducing conformational changes in the F ^o domain, thereby causing the rotation of adjacent subunits. This facilitates the phosphorylation of ADP → ATP |

Glycolysis

| Enzyme | Reaction | Requires/Produces | Regulation | Notes |
|--------------------------|--|---------------------------------------|--|---|
| Hexokinase | Glucose → Glucose-6-phosphate | Uses ATP for phosphorylation + energy | | Irreversible step (not committed) Hexokinase is nonspecific—phosphorylates glucose, galactose, fructose, and mannose. Present in all tissues. Low K_m (high affinity) Activated at any []. |
| Glucokinase | Glucose → Glucose-6-phosphate | Uses ATP for phosphorylation + energy | Regulated by the GKRP, where GK is sequestered in the nucleus and bound to GKRP when [glucose] is low. Once glucose is present in the cell in high [], GK is released to the cytoplasm to phosphorylate glucose to G6P. G6P then undergoes isomerization to F6P. High [F6P] induce the sequestering of GK in the nucleus. Activation: Insulin <i>well-fed state</i> Inhibition: Glucagon <i>fasting</i> | Irreversible step (not committed) Glucokinase is specific to glucose only. Present in the liver. Higher K_m than hexokinase Activated only at high []. |
| Phosphoglucose isomerase | Glucose-6-phosphate → Fructose-6-phosphate | – | | Reversible step |
| Phosphofructokinase-1 | Fructose-6-phosphate → fructose 1,6-bisphosphate | Uses ATP | Activation: Fructose-2,6-bisphosphate <i>activates glycolysis & inhibits gluconeogenesis</i> AMP <i>low-energy state</i> Insulin <i>well-fed state</i> Inhibition: ATP <i>high-energy state</i> Glucagon <i>fasting</i> Citrate <i>high TCA cycle activity, sufficient energy</i> | Irreversible step Committed step Rate-limiting step Last step of the preparative phase of glycolysis. |

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| | | | <i>production</i> H ⁺ Active oxidative phosphorylation, high energy production | |
| Aldolase | Fructose-1,6-bisphosphate → DHAP Fructose -1,6-bisphosphate → G3P | | | Reversible step |
| Triose phosphate isomerase | DHAP → G3P <i>Subsequent steps occur twice because we now have 2 G3Ps.</i> | | | Reversible step |
| Glyceraldehyde-3-phosphate | G3P + NAD ⁺ → NADH + 1,3-bisphosphoglycerate <i>Oxidation reduction reaction</i> | Produces NADH (cytosolic) | Inhibited by arsenate– a pentavalent As <i>competes with inorganic phosphate, directly affects ATP synthesis.</i> | Reversible step Adds inorganic phosphate without the need for ATP. |
| Glycerate Kinase | 1,3-bisphosphoglycerate → 3-phosphoglycerate | Produces ATP | | Reversible step |
| Phosphoglycerate Mutase | 3-phosphoglycerate → 2-phosphoglycerate <i>Isomerization</i> | | | Reversible step |
| Enolase | 2-phosphoglycerate → phosphoenolpyruvate <i>Dehydration</i> | | Fluoride (non physiological) inhibits enolase in bacterial glycolysis, preventing dental caries. | Reversible step |
| Pyruvate Kinase | PEP → pyruvate | Produces ATP | Activation: Fructose-1,6-bisphosphate <i>glycolytic intermediate</i> Insulin <i>well-fed state</i> Inhibition: ATP <i>high-energy state</i> Alanine <i>source of pyruvate via transamination rxn, high [pyruvate] inhibits glycolysis from running further.</i> Glucagon <i>fasting</i> | Irreversible step Most common glycolytic enzyme deficiency. Affects RBCs the most, compromising its structure → hemolytic anemia. |

Phosphorylation of Enzymes

| Enzyme | Phosphorylated | Dephosphorylated | Phosphorylated by | Effect |
|--|----------------|------------------|---|--|
| <u>Bifunctional enzyme:</u> Phosphofructokinase-2 | ACTIVE | INACTIVE | Insulin <i>well-fed state, green light for glycolysis</i> | Phosphorylates fructose-6-phosphate to fructose-2,6-bisphosphate, stimulating glycolysis. |
| <u>Bifunctional enzyme:</u> Fructose bisphosphatase-2 | INACTIVE | ACTIVE | Glucagon <i>Fasting state, glycolysis shouldn't run</i> | Removes a phosphate from fructose 2,6-bisphosphate, converting it to fructose-6-phosphate. → no stimulation of glycolysis. |
| Pyruvate Kinase | INACTIVE | ACTIVE | Glucagon <i>PKA phosphorylates pyruvate kinase, inhibiting glycolysis</i> | cAMP/PKA leads to the phosphorylation of pyruvate kinase, this inhibits glycolysis and promotes gluconeogenesis (makes sense in a fasting state) |
| Pyruvate Dehydrogenase Complex | INACTIVE | ACTIVE | PDH kinase Dephosphorylated by PDH phosphatase | |
| Glycogen Phosphorylase Kinase | ACTIVE | INACTIVE | Epinephrine (muscle and liver) and glucagon (liver) Dephosphorylated by insulin, activates phosphatase to inactivate glycogen degradation and stimulate glycogen synthesis. | Phosphorylates glycogen phosphorylase |
| Glycogen Phosphorylase | ACTIVE | INACTIVE | Glycogen phosphorylase kinase Phosphorylase kinase (IP3 pathway) In muscle cells, it is activated by AMP binding | Glycogen degradation |

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| | | | Dephosphorylated by insulin, activates phosphatase to inactivate glycogen degradation and stimulate glycogen synthesis. | |
| Glycogen Synthase | INACTIVE | ACTIVE | By cAMP/PKA pathway because of EP/glucagon. Calmodulin-dependent protein kinase (IP3 pathway) Phosphorylase kinase (IP3 pathway) | Glycogen synthesis is inhibited– remember the cell wouldn't allow two contradictory pathways to operate simultaneously |

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Pyruvate → Acetyl CoA

| Enzyme | Regulation | Deficiency |
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| PDH Complex | <p>Acetyl CoA- product inhibition <i>Directly binds to PDHC</i> NADH <i>NAD⁺ is needed, indicating that TCA cycle won't proceed either.</i></p> <p>Arsenite poisoning <i>produces a stable complex with lipoic acid</i></p> | <p>Deficiency in E1 is the most common cause of congenital lactic acidosis. X-linked Pyruvate accumulation, activating alternative pyruvate pathways: lactate production. Lactate production → lactic acidosis</p> |
| PDH Kinase | <p>Activation: ATP <i>high-energy state, phosphorylates PDHC and inactivates it.</i> Acetyl CoA (indirect activation) NADH</p> <p>Inhibition: Pyruvate <i>high [pyruvate] activates PDHC to fuel TCA cycle.</i></p> | <p>—</p> |
| PDH Phosphatase | <p>Activation: Calcium <i>signifies high activity in a muscle cell and a need for energy production.</i></p> | <p>—</p> |

Glycogen Metabolism

| Enzyme | Reaction | Regulation | Notes |
|--|--|---|---|
| Glucose-6-Phosphatase | Glucose-6-phosphate → glucose | <p>Activation (liver & muscle) Glucose-6-Phosphate <i>well-fed state</i></p> | <p>Deficiency (Von Gierke Disease):</p> <ul style="list-style-type: none"> - Affects liver, kindey, intestine (not muscle cells, because they dont have this enzyme) - Severe hypoglycemia - Hepatomegaly (fatty liver) - Growth retardation <i>brain requires glucose, and a quick supply of it.</i> - Progressive renal disease |
| Glycogen phosphorylase | Glycogen (n) → Glycogen (n-1) + Glucose-1-Phosphate | <p>Inhibition (Liver) Glucose-6-Phosphate <i>intermediate in the pathway</i> ATP <i>high-energy state</i> Glucose product <i>inhibition</i></p> <p>Inhibition (Muscle) G6P + ATP</p> <p>Activation (Muscle) Ca²⁺ <i>muscle contraction, need for energy</i> AMP <i>low-energy state</i></p> | <p>Deficiency (McArdle Syndrome)</p> <ul style="list-style-type: none"> - Only affects the muscle isoform - Weakness and cramping of muscle after exercise - No increase in lactate during exercise <i>no glucose → no pyruvate → no lactate</i> |
| Debranching enzyme (Transferase + α-1,6-Glucosidase) | <p>Transferase: transfers 4 glucose residues from a branch to the linear chain.</p> <p>α-1,6-Glucosidase: cleaves the branching glucose residue (α-1,6 linkage) and phosphorylates it to G1P</p> | – | – |
| Phosphoglucomutase | Glucose-1-Phosphate → Glucose-6-Phosphate | – | Reversible reaction In the cytosol |

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| UDP-Glucose Pyrophosphorylase | Glucose-1-Phosphate + UTP → UDP-Glucose + PPi | – | Reversible |
| Glycogen Synthase | Removes UDP from UDP-glucose + attaches glucose to glycogen fragment/glycogenin in a linear chain (no branches yet) | – | – |
| 4:6-Transferase | Cleaves a fragment of the linear chain and attaches it via an α -1,6 linkage (hence the name 4:6). Formation of branches. | – | – |

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يُرْبِي مِنَ الْيَيْسِ الْفُتَاتِ قُلُوبَا

Gluconeogenesis

| Enzyme | Reaction | Regulation | Location | |
|-----------------------------|--|--|---|---|
| Pyruvate Carboxylase | $\text{Pyruvate} + \text{ATP} + \text{CO}_2 + \text{NAD}^+ \rightarrow \text{Oxaloacetate} + \text{ADP} + \text{NADH}$ | Activated allosterically by acetyl CoA | Enzyme is found in both the mitochondria and the cytosol | Biotin <i>covalently attached</i> In the mitochondria |
| PEP Carboxykinase | $\text{Oxaloacetate} \rightarrow \text{PEP} + \text{CO}_2$ <i>Decarboxylation</i> | – | Occurs in the cytosol | OAA is reduced to malate, then oxidized to OAA again to be transported to the cytosol |
| Fructose-1,6-Bisphosphatase | $\text{F1,6B} \rightarrow \text{F6P}$ <i>Dephosphorylation</i> | Same allosteric regulators of the reverse reaction Activation: <i>Citrate TCA cycle operates (fatty acid degradation), signifying enough energy for gluconeogenesis</i> Inhibition: <i>AMP low-energy state, this pathway needs energy</i> <i>Fructose-2,6-bisphosphate activates PFK-1</i> | | |
| Glucose-6-Phosphatase | $\text{G6P} \rightarrow \text{Glucose}$ | – | In the ER lumen <i>translocase enters G6P into the ER, then GLUT 7 transports it to the cytosol.</i> | Not present in muscle cells |

Pyruvate → Ethanol (in yeast)

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|------------------------|---|---------------|
| Pyruvate Decarboxylase | Pyruvate → acetaldehyde <i>decarboxylation</i> | |
| Alcohol Dehydrogenase | Acetaldehyde + NADH → ethanol + NAD+ <i>Dehydrogenase</i> | Produces NAD+ |

Pyruvate → Lactate

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| Lactate Dehydrogenase | Pyruvate + NADH → lactate + NAD+ <i>Dehydrogenase</i> | Produces NAD+ Reversible reaction |
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وَالْعَبْدُ يَدْعُو وَالكَرِيمُ كَرِيمٌ

Metabolism of Mono & Disaccharides:

| Enzyme | Location | Mechanism | Product | Function | Deficiency | Notes |
|-------------------------------|--|--|---|--|--|--|
| Fructokinase | Liver, kidney, & small intestines | Phosphorylates fructose | Fructose → Fructose-1-Phosphate | F1P can then be converted into DHAP or glyceraldehyde which can become G3P and enter glycolysis. | A minor problem, because the fructose can still be metabolized by the nonspecific pathway. | Uses ATP. present in the specific fructose metabolism pathway. |
| Aldolase A | Present in most tissues | Cleaves fructose-1,6-bisphosphate | G3P | Produce an intermediate of glycolysis. | Aldolase B can catalyze the same reaction aldolase A can. | |
| Aldolase B | Liver, kidney, & small intestine | Cleaves fructose-1,6-bisphosphate & fructose-1-phosphate | G3P (nonspecific & glyceraldehyde (specific)) | Produce an intermediate of glycolysis. | No utilization of fructose-1-phosphate = loss of ATP for its phosphorylation. Glycolysis is activated to compensate for lost ATPs → hypoglycemia . Glycolysis → pyruvate → lactate → lactic acidosis . AMP increases, its accumulation stimulates its degradation. Degradation of purines produces uric acid → Hyperuricemia Reduced hepatic ATP → hepatic failure | |
| Aldose Reductase | Liver, kidney, retina, lens, Schwann cells, ovaries, seminal vesicles. | Reduces glucose into sorbitol, and oxidizes NADH to NAD ⁺ . | Glucose + NADH → Sorbitol + NAD ⁺ | | – | |
| Sorbitol Dehydrogenase | Ovaries, liver, seminal vesicles. | | Glucose → sorbitol → fructose | Direct conversion of glucose to fructose. | – | Fructose is sperm's main source of energy. |

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| <p>Galactokinase</p> | <p>–</p> | <p>Phosphorylates galactose</p> | <p>Galactose + ATP → Galactose-1-phosphate + ADP</p> | | <p>Galactose is trapped in the cell, which activates aldose reductase. Galactose is converted to polyalcohol–galactitol. It's trapped in the cell, causing water retention due to the messed up osmotic pressure. Fructose deficiency is less severe than galactokinase deficiency (no alt. pathway).</p> | |
| <p>GALT Galactose-1-Phosphate Uridyltransferase</p> | <p>–</p> | <p>A trade/exchange between Gal-1-P & UDP Gluc, and vice versa.</p> | <p>Gal-1-P + UDP Gluc. ↔ UDP Gal + Gluc-1- Phosphate</p> | <p>UDP-Gal can synthesize glycolipids, glycoproteins, GAGs, lactose. Gluc-1-phosphate is converted to G6P by phosphoglucomutase. In muscle cells (where no glucose-6-phosphatase is present), this is where this pathway ends. In liver cells, however, G6-phosphatase converts G6P→ glucose. Gluc-1-P can also react with UDP-glucose pyrophosphorylase to produce UDP-glucose and either is ¹used in glycogen synthesis or ²reacts with galactose.</p> | <p>Galactosemia, a genetic disease. ATP is used for the phosphorylation of galactose → increased [AMP] → hyperuricemia. Accumulation of galactose-1-phosphate & galactitol, causing cataracts & mental retardation, because of the damage/death of neurons.</p> | |
| <p>Epimerase</p> | <p>–</p> | <p>Epimerase galactose into glucose and vice versa.</p> | <p>UDP Gal ↔ UDP Glu</p> | <p>UDP Glu. can be used for glycogen synthesis when it is present in excess [].</p> | <p>–</p> | <p>–</p> |

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|---|-----------------------|-----------------------------|---|--|----------|--|
| <p>UDP-Glucose Dehydrogenase</p> | <p>–</p> | <p>Oxidizes UDP-Glucose</p> | <p>UDP-Glucose + NAD⁺ → UDP-Glucuronic acid + NADH</p> | <p>Glucuronic acid can be used to synthesize GAGs, or it can supply the pentose phosphate pathway.</p> | <p>–</p> | <p>–</p> |
| <p>Lactose Synthase</p> | <p>Mammary glands</p> | | <p>UDP-Galactose + Glucose → Lactose + UDP</p> | <p>Lactose synthase complex: Galactosyl transferase (Protein A): enzyme, transfers UDP-galactose to glucose and links them together. Alpha-lactalbumin (Protein B): not an enzyme, makes sure that protein A only uses glucose to ensure lactose synthesis, in mammary cells (selectivity). In other cells where protein B isn't present, there's no selectivity for what binds to UDP-galactose. Modified lactose forms such as N-acetyllactosamine (UDP-gal + N-acetylglucosamine), used for glycoproteins, glycolipids, GAGs.</p> | | <p>Lactose: Galactosyl β-1,4 Glucose</p> |

Alcohol Metabolism

| Enzyme | Reaction | Location | Notes |
|--|---|-----------------------------|---|
| Alcohol Dehydrogenase | $\text{Ethanol} + \text{NAD}^+ \rightarrow \text{Acetaldehyde} + \text{NADH}$ | Cytosol of hepatocytes | Responsible for 80-90% of ethanol metabolism (main pathway) Has 5 classes/isoenzymes, different isoforms are expressed in different tissues |
| Acetaldehyde Dehydrogenase | $\text{Acetaldehyde} + \text{NAD}^+ \rightarrow \text{Acetate} + \text{NADH}$ | Mitochondria of hepatocytes | |
| Acetyl CoA Synthetase | $\text{Acetate} \rightarrow \text{Acetyl CoA}$ | Muscle cells | |
| MEOS <i>Microsomal Ethanol Oxidizing System</i> | $\text{Ethanol} + \text{NADPH} + \text{H}^+ + \text{O}_2 \rightarrow \text{Acetaldehyde} + \text{NADP}^+ + 2\text{H}_2\text{O}$ | Hepatocytes | High K_m for ethanol- <i>induced by high [ethanol]</i> CYP2E1 is involved Responsible for 10-20% of ethanol metabolism Contributor of oxidative stress in hepatocytes due to the production of ROS (H_2O_2 , OH^\cdot , O_2^\cdot) |
| Catalase | $\text{Ethanol} + \text{H}_2\text{O}_2 \rightarrow \text{H}_2\text{O} + \text{Acetaldehyde}$ | Peroxisomes | Very minor pathway Very small % of ethanol metabolism Expressed by some microflora in the colon Relies on H_2O_2 |

اللّٰه يعطيكم العافية و يوفقكم و يرزقكم العلامات والسعي اللي ترضيكم يا رب
ادعوا لاختوتنا في كل بلاد المسلمين و مش غلط تدعولي كمان (:)