**Pyruvate Dehydrogenase & Krebs Cycle**

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[Regulation of pyruvate dehydrogenase](https://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb1/part2/krebs.htm#reg)
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**Pathway localization:**

**Glycolysis** enzymes are located in the **cytosol** of cells.  Pyruvate enters the **mitochondrion** to be metabolized further.

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| **Mitochondrial compartments:**The mitochondrial **matrix**contains Pyruvate Dehydrogenase and enzymes of Krebs Cycle, plus other pathways such as fatty acid oxidation.The mitochondrial **outer** **membrane** contains large **VDAC** channels, similar to bacterial [porin](https://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb1/part2/lipid.htm%22%20%5Cl%20%22porins) channels, making the outer membrane leaky to ions and small molecules. The **inner membrane** is the major permeability barrier of the mitochondrion. It contains various transport catalysts, including a carrier protein that allows pyruvate to enter the matrix. It is highly convoluted, with infoldings called cristae. Embedded in the inner membrane are constituents of the [respiratory chain](https://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb1/part2/redox.htm#respchain) and [ATP Synthase](https://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb1/part2/f1fo.htm). | https://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb1/part2/images/mito.gif |

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| **Pyruvate Dehydrogenase** catalyzes oxidative decarboxylation of pyruvate, to form acetyl-CoA. The overall reaction is shown at right. | https://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb1/part2/images/pyrudeh.gif |

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| Pyruvate Dehydrogenase is a **large complex** containing many copies of each of three enzymes, **E1**, **E2**, and **E3**. The structure of the complex is depicted in figures on p. 769 & 774 of Biochemistry, 3rd Edition, by Voet & Voet.The inner **core** of the mammalian Pyruvate Dehydrogenase complex is an **icosahedral** structure consisting of **60** copies of **E2**.At the **periphery** of the complex are:* **30** copies of **E1**(itself a tetramer with subunits 22) and
* **12** copies of **E3** (a homodimer), plus **12** copies of an **E3 binding protein** that links E3 to E2.

Prosthetic groups are listed below, a cartoon showing 3 subunits is at right, and a diagram summarizing the reactions catalyzed is on p. 770.  | https://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb1/part2/images/e1e2e3.gif |

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| **Enzyme** | **Abbreviated** | **Prosthetic Group** |
| **Pyruvate Dehydrogenase** | **E1** | **Thiamine pyrophosphate (TPP)** |
| **Dihydrolipoyl Transacetylase** | **E2** | **Lipoamide** |
| **Dihydrolipoyl Dehydrogenase** | **E3** | **FAD** |

**FAD** (**F**lavin**A**denine**D**inucleotide) is a derivative of the B-vitamin riboflavin (dimethylisoalloxazine-ribitol). The flavin ring system undergoes **oxidation/reduction** as shown below. Whereas NAD+ is a coenzyme that reversibly binds to enzymes, FAD is a **prosthetic group**, that is permanently part of the complex.

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| FAD accepts and donates 2 electrons with 2 protons (2 H):**FAD + 2 e- + 2 H+ �� FADH2** | https://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb1/part2/images/fad.gif |

**Thiamine pyrophosphate** (**TPP**) is a derivative of  thiamine (vitamin B1). Nutritional deficiency of thiamine leads to the disease **beriberi**. Beriberi affects especially the brain, because TPP is required for carbohydrate metabolism, and the brain depends on glucose metabolism for energy.

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| https://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb1/part2/images/tpp.gif A proton readily dissociates from the **C** that is between **N** and **S** in the thiazole ring of TPP. The resulting**carbanion** (ylid) can attack the electron-deficient keto carbon of  pyruvate. See also diagram p. 771. | https://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb1/part2/images/pyruvate.gif |

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| **Lipoamide** includes a **dithiol** that undergoes oxidation and reduction. The carboxyl group at the end of lipoic acid's hydrocarbon chain forms an **amide bond** to the side-chain amino group of a lysine residue of **E2**.A **long flexible arm**, including hydrocarbon chains of lipoate and the lysine R-group, links the dithiol of each lipoamide to one of two lipoate-binding domains of each **E2**. Lipoate-binding domains are themselves part of a **flexible strand of E2** that extends out from thecoreof the complex.The long flexible attachment allows **lipoamide** functional groups to **swing** back and forth between **E2**active sites in the core of the complex and active sites of **E1** & **E3** in the outer shell of the complex.The **E3 binding protein** (that binds E3 to E2) also has attached**lipoamide** that can exchange reducing equivalents with lipoamide on E2.For **diagrams** showing the approximate arrangement of functional domains, based on structural studies of Pyruvate Dehydrogenase and a related enzyme see: * a [website](http://www.bmsc.washington.edu/WimHol/figures/figs5/WimFigs5.html) of the laboratory of Wim Hol.
* an [article](http://dx.doi.org/doi%3A10.1074/jbc.M504363200) by Milne et al. (Fig. 5, requires a subscription to J. Biol. Chem.).
 | https://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb1/part2/images/lipoic.gif |

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| **Organic arsenicals** are potent inhibitors of lipoamide-containing enzymes such as Pyruvate Dehydrogenase. These highly toxic compounds react with "vicinal" dithiols such as the functional group of lipoamide as shown at right. | https://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb1/part2/images/arsenic.gif |

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| In the overall reaction, the acetic acid generated is transferred to **coenzyme A**. The final electron acceptor is **NAD+**. Complete [structures](https://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb1/part2/bioener.htm#coa) of these coenzymes are presented in the section on bioenergetics. | https://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb1/part2/images/accoa.gif | https://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb1/part2/images/nad.gif |

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| The sequence of reactions catalyzed by the Pyruvate Dehydrogenase complex is summarized in Fig. 21-6 p. 770, and in the animation at right. The mechanism is depicted in greater detail on p. 771-772.The reaction proceeds as follows: | [https://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb1/part2/images/animat.gif](https://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb1/part2/krebs.htm#animat1)**of Pyruvate Dehydrogenase** |

1. The keto carbon of **pyruvate** reacts with the carbanion of **TPP** on **E1** to yield an addition compound. The electron-pulling positively charged nitrogen of the thiazole ring promotes loss of CO2. What remains is **hydroxyethyl-TPP**.
2. The hydroxyethyl carbanion on TPP of **E1** reacts with the disulfide of **lipoamide** on **E2**. What was the keto carbon of pyruvate is oxidized to a carboxylic acid, as the disulfide of lipoamide is reduced to a dithiol. The **acetate** formed by oxidation of the hydroxyethyl moiety is linked to one of the thiols of the reduced lipoamide as a **thioester** (**~**).
3. The acetate is transferred from the thiol of lipoamide to the thiol of **coenzyme A**, yielding **acetyl CoA**.
4. The reduced lipoamide swings over to the **E3**active site. Dihydrolipoamide is reoxidized to the disulfide, as 2 e- + 2 H+ are transferred to a disulfide on E3 (disulfide interchange).
5. The dithiol on E3 is reoxidized as 2 e- + 2 H+ are transferred to **FAD**. The resulting FADH2 is reoxidized by electron transfer to **NAD+**, to yield **NADH + H+**.

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| **Acetyl CoA**, a product of the Pyruvate Dehydrogenase reaction, is a central compound in metabolism. The "high energy" thioester linkage makes it an excellent donor of the acetate moiety. | https://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb1/part2/images/acetylcoa.gif |

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| For example, acetyl CoA functions as:* input to the Krebs Cycle, where the acetate moiety is further degraded to CO2.
* donor of acetate for synthesis of [fatty acids](https://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb2/part1/fasynthesis.htm), [ketone bodies](https://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb2/part1/fatcatab.htm#ketone), and [cholesterol](https://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb2/part1/cholesterol.htm).

**Regulation** of Pyruvate Dehydrogenase complex (see also p. 780-781): | https://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb1/part2/images/acetcoa.gif |

**Product inhibition by NADH and acetyl CoA:**NADH competes with NAD+ for binding to **E3**. Acetyl CoA competes with Coenzyme A for binding to **E2**.

**Regulation by phosphorylation/dephosphorylation of E1:** Specific regulatory Kinases and Phosphatases are associated with the Pyruvate Dehydrogenase complex within the mitochondrial matrix.

* **Pyruvate Dehydrogenase Kinases** catalyze phosphorylation of serine residues of **E1**, **inhibiting** the complex.
* **Pyruvate Dehydrogenase** **Phosphatases** reverse this inhibition.

**Pyruvate Dehydrogenase Kinases** are **activated by** **NADH** and **acetyl-CoA**, providing another way the two major products of the Pyruvate Dehydrogenase reaction inhibit the complex. Pyruvate Dehydrogenase Kinase activation involves **interaction with E2** subunits to sense changes in oxidation state and acetylation of lipoamide caused by NADH and acetyl-CoA.

During **starvation**, **Pyruvate Dehydrogenase Kinase increases** in amount in most tissues, including skeletal muscle, via increased gene transcription. Under the same conditions, the amount of Pyruvate Dehydrogenase Phosphatase decreases. The resulting**inhibition of Pyruvate Dehydrogenase** prevents muscle and other tissues from catabolizing glucose and gluconeogenesis precursors. Metabolism shifts toward fat utilization, while muscle protein breakdown to supply gluconeogenesis precursors is minimized, and available glucose is spared for use by the brain.

A **Ca++-sensitive**isoform of the **phosphatase** that removes phosphate residues from **E1** is expressed in muscle cells. The increased cytosolic Ca++ that occurs during activation of muscle contraction can lead to Ca++ uptake by mitochondria. The higher Ca++ **stimulates**the**phosphatase**, and dephosphorylation **activates Pyruvate Dehydrogenase**. Thus mitochondrial metabolism may be stimulated during **exercise**.

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| **Lecture notes** relating to **Krebs Cycle** are not provided in the usual format, because lectures will be presented by students. Some questions on Krebs Cycle are included in the self-study quiz for this class.Select the **interactive tutorial** at right for information about the Krebs Citric Acid Cycle. Within the tutorial, drag the cursor over each enzyme name for information about that reaction.Note that **FADH2**, listed as a product of **succinate** oxidation, is reoxidized to FAD as redox carriers within the Succinate Dehydrogenase complex pass electrons to **coenzyme Q** of the [respiratory chain](https://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb1/part2/redox.htm#comp2). Thus it would be more appropriate to list **coenzyme** **QH2** as a product of the Succinate Dehydrogenase reaction. The initial acceptor, FAD, is included in the diagram for consistency with most textbooks. | https://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb1/part2/images/krebsbut.gif |

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**Pathway localization:**

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* an [article](http://dx.doi.org/doi%3A10.1074/jbc.M504363200) by Milne et al. (Fig. 5, requires a subscription to J. Biol. Chem.).
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| **Organic arsenicals** are potent inhibitors of lipoamide-containing enzymes such as Pyruvate Dehydrogenase. These highly toxic compounds react with "vicinal" dithiols such as the functional group of lipoamide as shown at right. | https://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb1/part2/images/arsenic.gif |

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| In the overall reaction, the acetic acid generated is transferred to **coenzyme A**. The final electron acceptor is **NAD+**. Complete [structures](https://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb1/part2/bioener.htm#coa) of these coenzymes are presented in the section on bioenergetics. | https://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb1/part2/images/accoa.gif | https://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb1/part2/images/nad.gif |

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| For example, acetyl CoA functions as:* input to the Krebs Cycle, where the acetate moiety is further degraded to CO2.
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**Regulation** of Pyruvate Dehydrogenase complex (see also p. 780-781): | https://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb1/part2/images/acetcoa.gif |

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