Journal of Evolution and Health: A joint publication of the Ancestral Health Society and the Society for Evolutionary Medicine and Health

Title

Ketogenic Diets and Energy Metabolism in Cancer

Journal

Journal of Evolution and Health: A joint publication of the Ancestral Health Society and the Society for Evolutionary Medicine and Health, 3(1)

Authors

Feinman, Richard D.
Miller, Anna
Fine, Eugene J.

Publication Date

2018

DOI

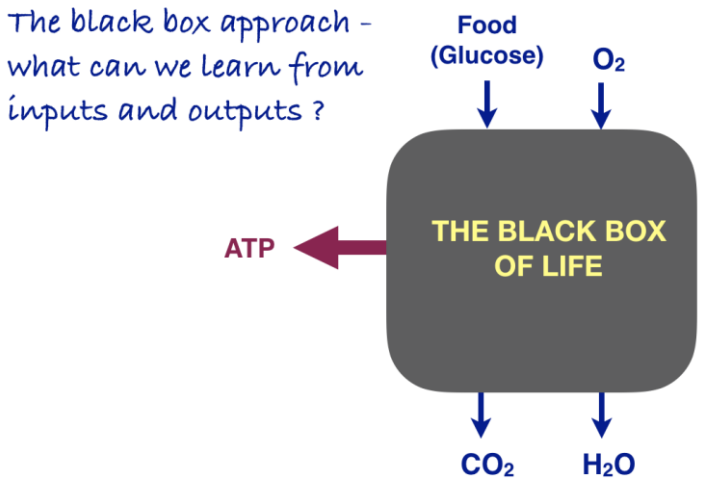
10.15310/2334-3591.1100

Peer reviewed

Alterations in energy metabolism constitute one of the large changes that cells undergo in conversion to the cancerous state. Ketone bodies represent a substantially under-investigated energy source and ketogenic diets show promise for correction or prevention of the altered metabolic state of cancers. The original observations of Otto Warburg on the energetics of the tumor provide a conceptual framework for current research.

Warburg found that cancer cells produced a higher ratio of lactic acid to CO_2 than normal cells. His interpretation was that cancer cells had an increased reliance on glycolysis (anaerobic metabolism) as opposed to aerobic respiration and he thought that this was a characteristic of all cancer cells. While it turned out not to be that simple, many if not most tumors do show a Warburg effect. Much cancer research might be described as a hunt for the points of disruption in the aerobic and/or anaerobic metabolism – or, most likely, the connection between them. Here we review broad outlines of energetic mechanisms with an eye on the Warburg effect and how ketone bodies might make a difference.

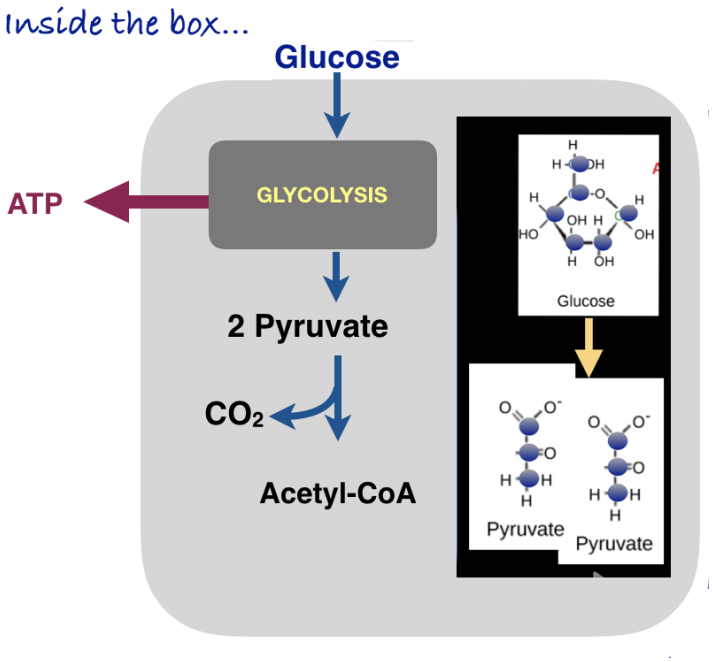
Start from the beginning. The black box of life takes food (glucose for simplicity) and oxygen as inputs and puts out CO_2 and water. The net effect is to produce energy in the form of ATP.



A look inside the black box shows individual processes. Glycolysis converts glucose to two molecules of the three-carbon compound pyruvate. This is the branch point. Pyruvate has many fates, providing the major substrate for aerobic energy metabolism as well as providing the starting point for gluconeogenesis and, in its conversion to lactate, an indicator of dependence on anerobic metabolism.

Pyruvate can be oxidized to acetyl-CoA, the derivative of acetic acid that is the substrate for oxidative metabolism in the tricarboxylic acid cycle (TCA cycle;

Krebs cycle). In cells that don't carry out respiration (red blood cells, rapidly exercising muscle) or under conditions of reduced oxygen (hypoxic environment of many cancer cells), pyruvate can be reduced to lactate.

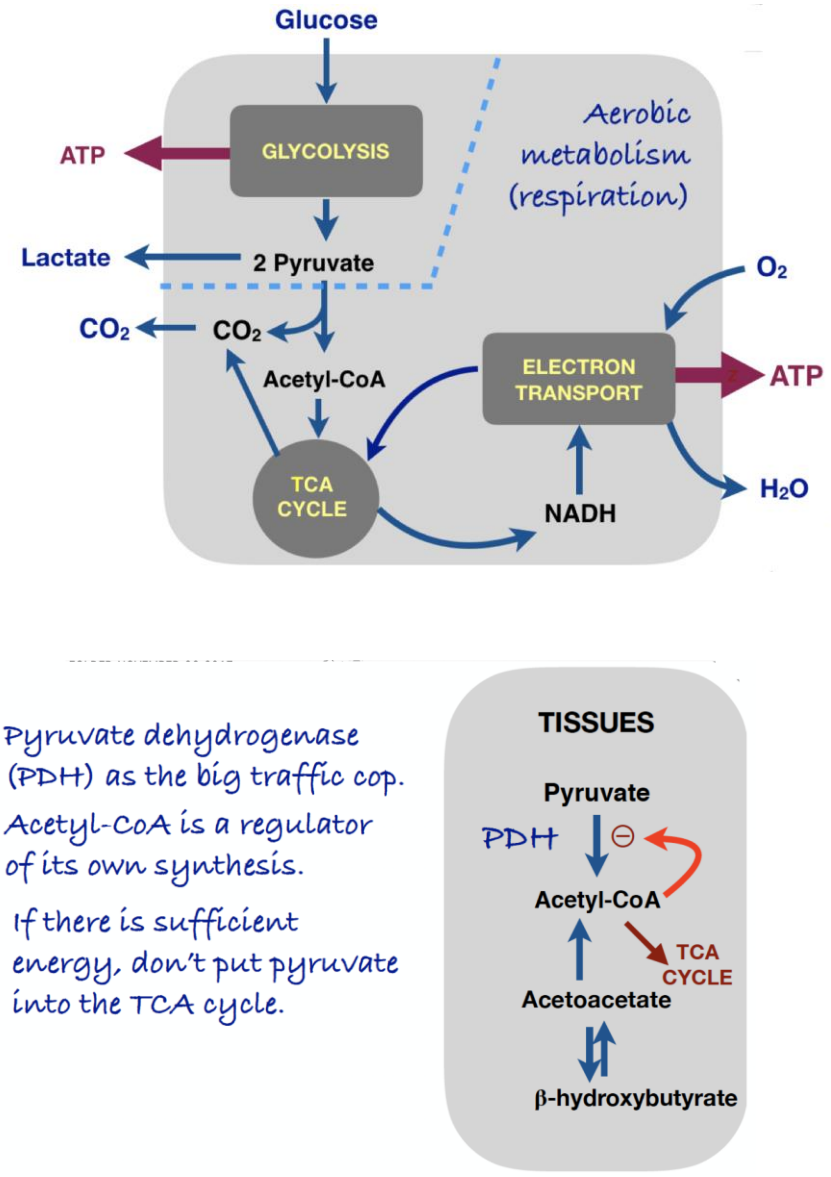


Acetyl-CoA is also supplied by fatty acids. Under conditions of low total caloric or low carbohydrate input, the liver converts acetyl CoA to the ketone bodies β-hydroxy butyrate and acetoacetate. The ketone bodies are transported to peripheral tissues where they are, in effect, converted back to acetyl-CoA; the function of the ketone bodies is to transport acetyl-CoA from liver to the tissues.

In the TCA cycle Acetyl-CoA is oxidized to CO_2 by the oxidative coenzyme NAD^+. The product NADH is oxidized in the electron transport chain (ETC) where a "bucket-brigade" of proteins in the mitochondrial membrane allow transfer of reducing power sequentially, ultimately to molecular oxygen (where the H_2O comes from in the black box). The high-energy state that is generated is due to a membrane H^+ gradient; that is, the effect of the oxidation moves protons to the outside of the inner mitochondrial membrane. Dissipation of the gradient through the F_1F_O particle in the mitochondrial membrane generates ATP. The overall process is called *oxidative phosphorylation* (*OxPhos*).

DOI: 10.15310/2334-3591.1100

Pyruvate dehydrogenase (PDH), the enzyme that converts pyruvate to acetyl-CoA, is the big traffic cop. Acetyl-CoA, the product of the reaction, feeds back to turn off its own production. This ensures that if acetyl-CoA is already high (from fat or ketone bodies), any pyruvate (from amino acids, for example) will be channeled into gluconeogenesis or other processes.



Several kinds of metabolic inhibitors aid in the characterization of mechanism. *OxPhos inhibitors*, such as oligomycin, knock out ATP production by preventing utilization of the gradient. (The 'O' in F_1F_O stands for oligo). This stops the

whole oxidative process. Any remaining ATP generated must come from glycolysis. *Uncouplers* (e.g. *FCCP),* as the name implies, separate the oxidation of substrate in the ETC from ATP production. The mechanism is to destroy the high-energy state of the membrane by allowing unproductive passage of H^+ back into the mitochondrion. Oxidation of acetyl CoA will continue — actually increases because, not coupled to anything, it will run free — but no ATP can be made. *Glucose uptake* can be blocked by inhibitors such as the drug *cytochalasin B* or analogs such as *2-deoxyglucose*.

We have previously shown that one of the ketone bodies, acetoacetate, will inhibit both growth and ATP productionin several cancer lines [1]. A normal fibroblast line served as control and was not affected by acetoacetate. We have more recently shown that glucose uptake in several lines is inhibited as much by acetoacetate as by cytochalasin. Our preliminary results with inhibitors showed a reduction in aerobic metabolism — lower oxygen uptake and smaller inhibition when treated with oligomycin but, at the same time, we observed a lower glycolytic effect — smaller lactic acid and impaired ability to compensate for inhibition of respiration with oligomycin. Whether the latter effect might indicate a way to target the oxidative glycolysis, as it is called, or, generally, whether the effects represent multiple responses or arise from a single reaction with acetoacetate is the target of future research.

1. Fine EJ, Miller A, Quadros EV, Sequeira JM, Feinman RD: **Acetoacetate reduces growth and ATP concentration in cancer cell lines which over-express uncoupling protein 2.** *Cancer Cell Intl* 2009, **9**:14 http://www.cancerci.com/content/9/1/14