Cori Cycle

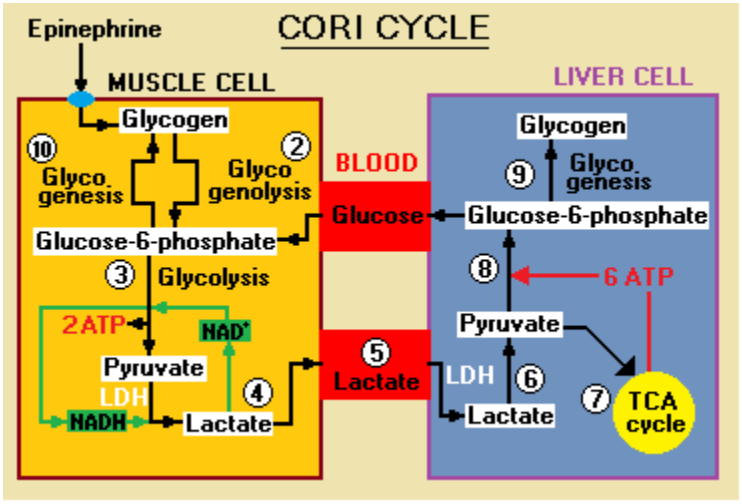
When oxygen supply is insufficient, typically during intense muscular activity, energy must be released through anaerobic metabolism. Lactic acid fermentation converts pyruvate to lactate by lactate dehydrogenase. Most important, fermentation regenerates NAD^+, maintaining the NAD^+ concentration so that additional glycolysis reactions can occur. The fermentation step oxidizes the NADH produced by glycolysis back to NAD^+, transferring two electrons from NADH to reduce pyruvate into lactate.Muscular activity or its anticipation leads to the release of epinephrine by the adrenal medulla.

Epinephrine markedly stimulates glycogen breakdown(glycogenolysis) in muscles and, to a lesser extent, in the liver. Muscular activity quickly uses stored ATP as the energy source and more ATP must be generated by the breakdown of glycogen. The sequence of epinephrine stimulating events is an exemple of “signalling cascade” outlined in the following sequence.

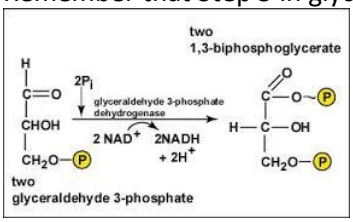
1) Epinephrine binds to a receptor on the muscle cell membrane. The receptor undergo a conformational change.
2) The coupled G-protein changes its conformation too and it exchanges GDP with GTP.
3) Subunit α detaches from G-protein and stimulates adenyl cyclase in the membrane.
4) Adenyl cyclase catalyzes the formation of cyclic AMP from ATP.
5) The increase of cyclic AMP in cytosol activates Protein Kinase A. The binding of cyclic AMP forces the control subunits to separate from the catalytic subunits, the enzyme is "switched on" for activity.
6) PKA causes phosphorylations (addition of phosphate) on a series of phosphorylation enzymes. This activates them to breakdown glycogen and finally produce glucose-1-phosphate.
7) At the same time phosphrylation enzymes are activated, glycogen synthetase enzymes must be inactivated. Glycogenesis must be "switched off" while glycogenolysis is "switched on."

Glucose-6-phosphate is the final result of the initial stimulation by epinephrine as well as by other hormones such as glucagon. If this happened to a muscle cell, then the glycolysis pathway is the next step in the sequence. If this happened to a liver cell stimulated by glucagon, then glucose is produced to enter the blood stream.

During muscle contractions, ATP is constantly being used to supply energy and more ATP is produced to replenish supplies.
At first glycolysis produces pyruvate which is then converted into acetyl CoA and is metabolized in the citric acid cycle to make ATP using the electron transport chain.
If muscular activity continues, the availability of oxygen for use at the end of the electron transport chain becomes the limiting factor and the cells soon exhaust their supplies of oxygen. As a consequence NADH molecules are not oxydized anymore and coenzyme NAD^+ is produced no more. When this happens, the citric acid cycle is inhibited because there is no way to oxydize its metabolites and pyruvate accumulates in the cell. However, glycolysis continues even under anaerobic conditions even though the citric acid cycle works only under aerobic conditions.



Epinephrine at (1) stimulates the enzymes to work on glycogen as discussed above.
Glycogenolysis at (2) is stimulated to make more glucose-6-phosphate.
When the cells become anaerobic, glycolysis (3) continues if pyruvate is converted to lactate (4).
Remember that Step 5 in glycolysis requires NAD^+ to be reduced to NADH.



STEP 5 in glycolysis.

As just said above, this coenzyme is oxydized back to NAD^+ during the oxydative phosphorilation and this process stops in case of oxygen lack.
The synthesis of lactate from pyruvate supplies this deficiency of NAD^+. It is catalized by LDH. It requires NADH and produces NAD^+ so that Step 5 can continue.
The formation of lactate "buys time" and shifts part of the metabolic burden to the liver.

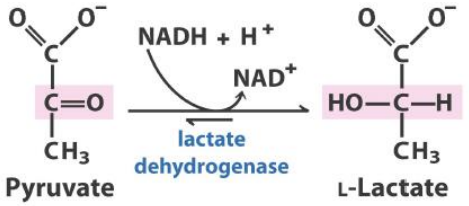
Even though not as much ATP can be furnished by glycolysis alone (2 ATP molecules each glucose molecule), this pathway is a significant source of ATP when muscular activity continues for any length of time. The final limiting factor in continued muscular activity is the build up of lactic acid. The lactic acid eventually produces muscular pain and cramps which force discontinuation of activity. Usually before this happens and after activity has ceased, lactic acid diffuses out of the muscle cells and into the blood where it enters the liver.
The body is very efficient in that lactate is sent in the bloodstream (5) and reaches the liver which can convert it back to pyruvate (6) and then to glucose through gluconeogenesis (8). Glucose can enter the bloodstream (9) and be carried to muscles and immediately used. If by this time the muscles have ceased activity, the glucose can be used to rebuild supplies of glycogen through glycogenesis (10).

This recycling of lactic acid is referred to as the Cori Cycle. The Cori cycle also operates more efficiently when the muscular activity has stopped. At this time the oxygen debt can be made up so that the citric cycle and electron transport chain also begin to function again. In order for most of the lactate to be converted to glucose, some must be converted to pyruvate and then to acetyl CoA (7). The citric acid cycle and electron transport chain must provide ATP to "fuel" the gluconeogenesis of the remainder of the lactic acid to glucose.

Overall, the glycolysis part of the cycle produces 2 ATP molecules at a cost of 6 ATP molecules consumed in the glycogenesis part. Each iteration of the cycle must be maintained by a net consumption of 4 ATP molecules. As a result, the cycle cannot be sustained indefinitely. The intensive consumption of ATP molecules indicates that the Cori cycle shifts the metabolic burden from the muscles to the liver.

RIASSUMENDO

FERMENTAZIONE LATTICA



$\Delta G'^{\circ} = -25.1$ kJ/mol

Quindi, le conseguenze importanti della fermentazione lattica sono:

1. Rigenerazione di NAD^+ per alimentare la glicolisi e continuare così il processo di demolizione del glucosio, anche se con rese energetiche minori
2. ATP prodotto "in loco" (fosforilazione a livello del substrato) può essere utilizzato direttamente e con rapidità nella cellula muscolare
3. La glicolisi avviene nella fibra muscolare in maniera autonoma rispetto alle concentrazioni di O_2 nel sangue

SVANTAGGI:
L'acido lattico viene smaltito molto lentamente e produce abbassamento del pH sia nel muscolo che nel sangue (dolore, affaticamento fisico, blocco muscolare)