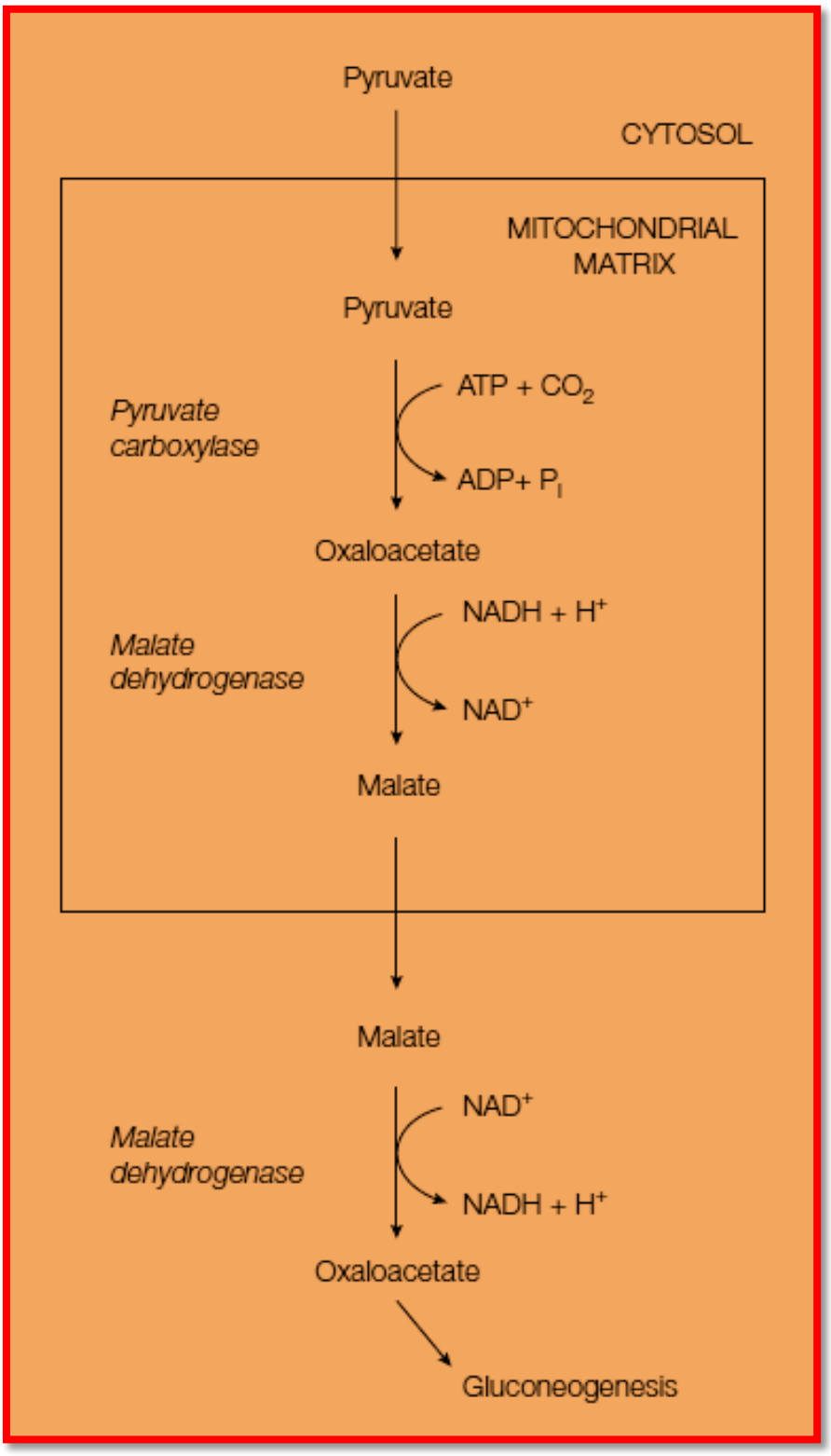
Gluconeogenesis (Part II.)

Transport of Oxaloacetate



- Pyruvate is first transported from the cytosol into mitochondria, where it is converted into oxaloacetate by Pyruvate carboxylase enzyme (mitochondrial matrix enzyme).
- Oxaloacetate produced by pyruvate carboxylase needs to exit the mitochondrion. However the inner mitochondrial membrane is not permeable to this compound.
- Thus oxaloacetate is converted to malate inside the mitochondrion by mitochondrial malate dehydrogenase.
- The malate is transported through the mitochondrial membrane by a special transport protein and then the malate is converted back to oxaloacetate in the cytoplasm by a cytoplasmic malate dehydrogenase.

Reciprocal regulation of glycolysis and gluconeogenesis

- Glycolysis generates two ATPs net per glucose whereas gluconeogenesis uses four ATPs and two GTPs per glucose.
- Thus, if both glycolysis and gluconeogenesis were allowed to operate simultaneously, converting glucose to pyruvate and back again, the only net result would be the utilization of two ATPs and two GTPs.
- This is prevented by tight coordinate regulation of glycolysis and gluconeogenesis.
- Since many of the steps of the two pathways are common, the steps that are distinct in each pathway are the sites of this regulation, in particular the inter conversions between fructose 6-phosphate and fructose 1,6-bisphosphate and between PEP and pyruvate.

Regulation of PFK and fructose 1, 6-bisphosphatase

- When the level of AMP is high, this indicates the need for more ATP synthesis. AMP stimulates PFK, increasing the rate of glycolysis, and inhibits fructose 1,6- bisphosphatase, turning off gluconeogenesis.
- Conversely, when ATP and citrate levels are high, this signals that no more ATP need be made.

- ATP and citrate inhibit PFK, decreasing the rate of glycolysis, and citrate stimulates fructose 1,6- bisphosphatase, increasing the rate of gluconeogenesis.

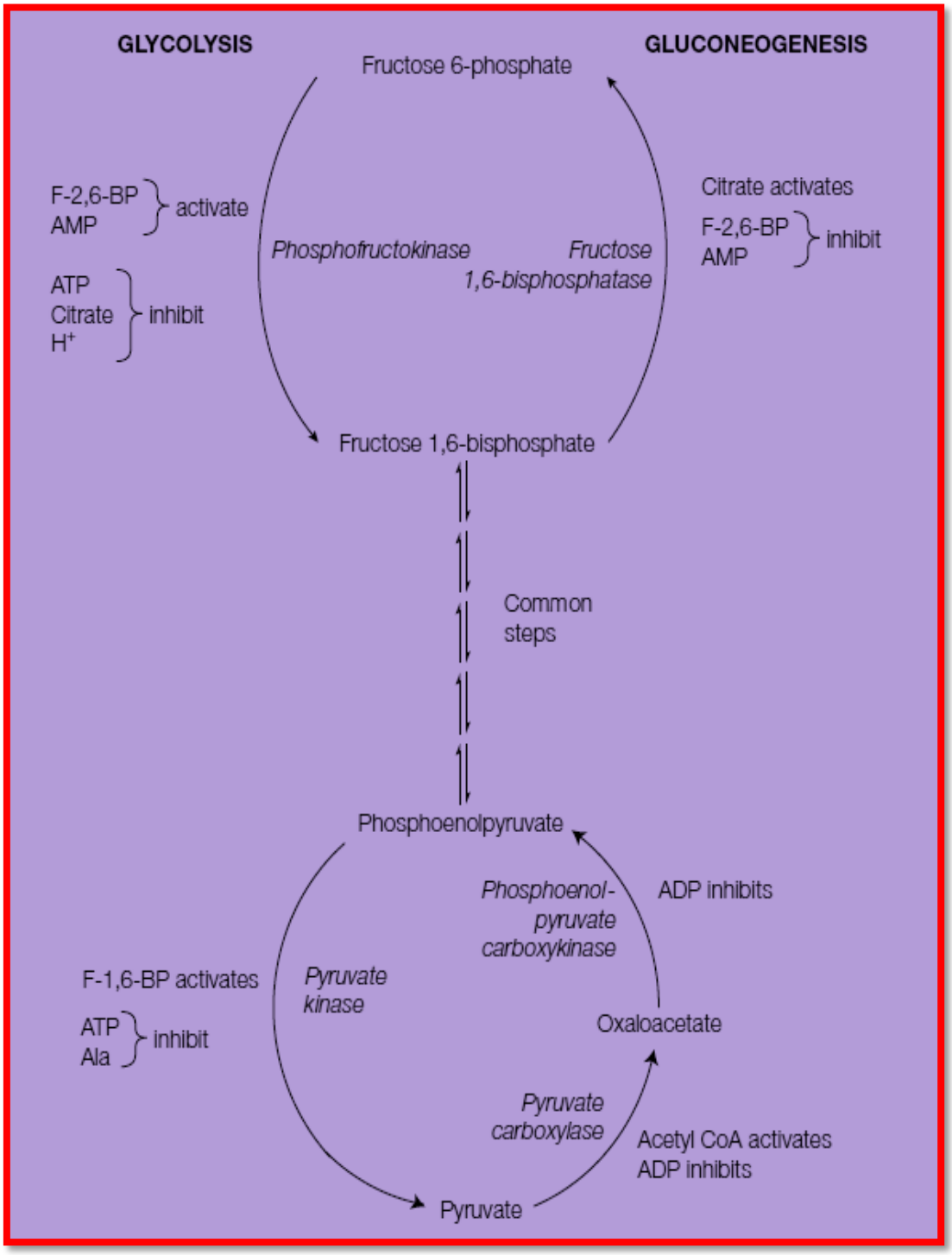


Fig. Reciprocal regulation of glycolysis and gluconeogenesis.

Regulation of pyruvate kinase / pyruvate carboxylase / PEP carboxykinase

- In liver, pyruvate kinase is inhibited by high levels of ATP and alanine so that glycolysis is inhibited when ATP and biosynthetic intermediates are already plentiful.
- Acetyl CoA is also abundant under these conditions and activates pyruvate carboxylase, favoring gluconeogenesis.
- Conversely, when the energy status of the cell is low, the ADP concentration is high and this inhibits both pyruvate carboxylase and PEP carboxykinase, switching off gluconeogenesis. At this time, the ATP level will be low so pyruvate kinase is not inhibited and glycolysis will operate.
- Pyruvate kinase is also stimulated by fructose 1,6-bisphosphate so that its activity rises when needed, as glycolysis speeds up.

The Cori cycle

- During vigorous exercise under the limiting oxygen conditions, the formation of NADH by glycolysis exceeds the ability of the respiratory chain to oxidize it back to NAD+.
- The pyruvate produced by glycolysis in muscle is then converted to lactate by lactate dehydrogenase, a reaction that regenerates NAD+ and so allows glycolysis to continue to produce ATP.
- However, lactate is a metabolic dead-end in that it cannot be metabolized further until it is converted back to pyruvate.
- Lactate diffuses out of the muscle and is carried in the bloodstream to the liver. Here it diffuses into liver cells and is converted back to pyruvate by lactate dehydrogenase.
- The pyruvate is then converted to glucose by gluconeogenesis and the glucose is released back into the bloodstream ready to be taken up by skeletal muscle (and brain).
- This cycle of reactions is called the Cori cycle.

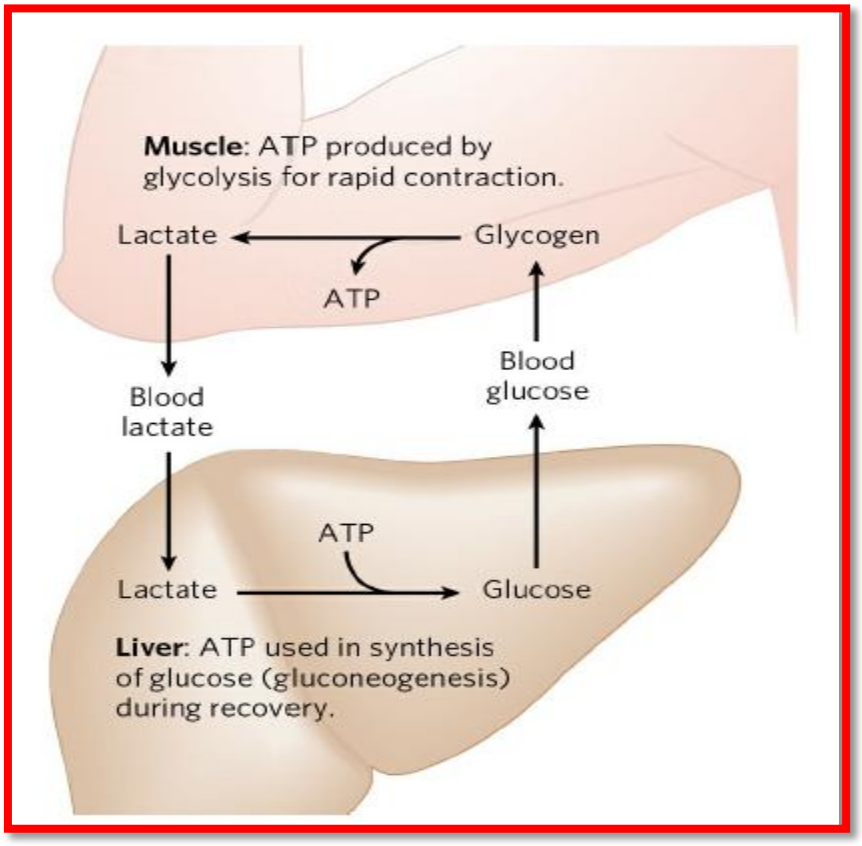


Fig. The Cori cycle.