Cori cycle/ Lactic acid cycle

- Given by Carl F. Cori and Gerty T. Cori
- The metabolic product of glucose formed in tissues i.e. lactate, formed by glycolysis in skeletal muscle and erythrocytes, is transported to the liver and kidney where it re-forms glucose, which again becomes available via the circulation for oxidation in the tissues. This process is known as the Cori cycle, or lactic acid cycle.
- Under aerobic conditions,
- $\text{Glucose} \xrightarrow[\text{Glycolysis}]{} \text{Pyruvate} \xrightarrow[\text{TCA cycle}]{} \text{NADH, } FADH_2 \longrightarrow 32 \text{ ATP}$
- Under anaerobic conditions (during vigorous exercise in muscles),
- $\text{Glucose} \xrightarrow[\text{Glycolysis}]{} \text{Pyruvate} \longrightarrow 2 \text{ ATP}$
- In anaerobic conditions, no TCA cycle will occur after pyruvate formation from glucose, as there is no O_2, which is terminal electron acceptor, therefore, Electron transport chain will not occur.
- Muscles require energy to do exercise and each glucose molecule is only producing 2 ATP molecules.
- Blood lactate conversion to glucose via pyruvate in liver is at expense of 6 ATP molecules

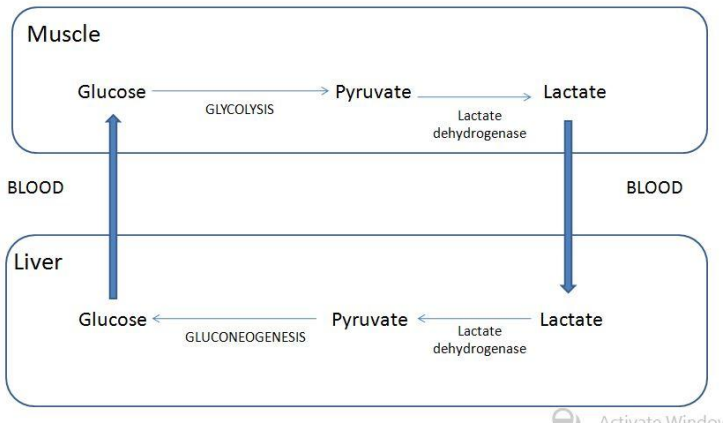

Fig 1. Cori cycle/ Lactic acid cycle.

- Significance: Cori cycle prevents lactic acidosis (excessive accumulation of lactate) in muscle under anaerobic conditions. This cycle is also important for production of energy molecule (ATP) during muscle activity, as muscles get deprived of energy due to insufficient glucose. Thus, Cori cycle help in proper functioning of muscle by suppying reqired energy in the form of glucose.

- Carl and Gerty Cori shared the Nobel Prize in Physiology or Medicine in 1947 with Bernardo Houssay of Argentina, who was cited for his studies of hormonal regulation of carbohydrate metabolism.

- The enzymatic defect in von Gierke disease was elucidated in 1952 by Carl and Gerty Cori. They found that glucose 6-phosphatase is missing from the liver of a patient with this disease. Glucose-6-phosphatase is an enzyme involved in gluconeogenesis, which carry out hydrolysis of glucose 6-phosphate to form glucose. This was the first demonstration of an inherited deficiency of a liver enzyme. The liver glycogen is normal in structure but present in abnormally large amounts. The absence of glucose 6-phosphatase in the liver causes hypoglycemia because glucose cannot be formed from glucose 6-phosphate. This phosphorylated sugar does not leave the liver, because it cannot cross the plasma membrane. The presence of excess glucose 6-phosphate triggers an increase in glycolysis in the liver, leading to a high level of lactate and pyruvate in the blood. Patients who have von Gierke disease also have an increased dependence on fat metabolism. This disease can also be produced by a mutation in the gene that encodes the glucose 6-phosphate transporter.

GABA shunt pathway

GABA and L-glutamate are the most abundant neurotransmitters in mammalian brain. While GABA is the major inhibitory neurotransmitter, L-glutamate is an excitatory neurotransmitter. Both are key mediators of synaptic plasticity and neuroendocrine function.

Disturbances in the homeostasis of GABA in the brain are implicated in the development of epilepsy, depression, Parkinson's disease, Huntington's chorea, Alzheimer's disease, and Stiff-Man syndrome.

The GABA shunt is a closed-loop process with the dual purpose of producing and conserving the supply of GABA. GABA is present in high concentrations (millimolar) in many brain regions. These concentrations are about 1,000 times higher than concentrations of the classical monoamine neurotransmitters in the same regions. This is in accord with the powerful and specific actions of GABAergic neurons in these regions. Glucose is the principal precursor for GABA production in vivo, although pyruvate and other amino acids also can act as precursors. The first step in the GABA shunt is the transamination of α-ketoglutarate, formed from glucose metabolism in the Krebs cycle by GABA α-oxoglutarate transaminase (GABA-T) into l-glutamic acid. Glutamic acid decarboxylase (GAD) catalyzes the decarboxylation of glutamic acid to form GABA. GAD appears to be expressed only in cells that use GABA as a neurotransmitter. GABA is metabolized by GABA-T to form succinic semialdehyde. To conserve the available supply of GABA, this transamination generally occurs when the initial parent compound, α-ketoglutarate, is present to accept the amino group removed from GABA, reforming glutamic acid. Therefore, a molecule of GABA can be metabolized only if a molecule of precursor is formed. Succinic semialdehyde can be oxidized by succinic semialdehyde dehydrogenase (SSADH) into succinic acid and can then reenter the Krebs cycle, completing the loop (Figure 16-1).

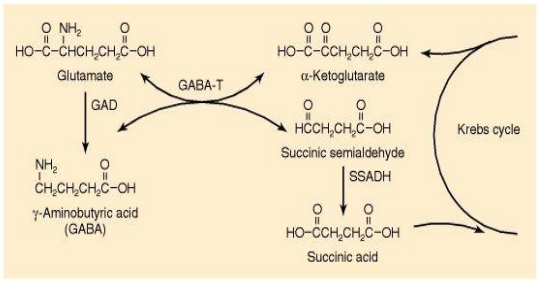

Figure 16-1

GABA shunt reactions are responsible for the synthesis, conservation and metabolism of GABA. *GABA-T*, GABA α-oxoglutarate transaminase; *GAD*, glutamic acid decarboxylase; *SSADH*, succinic semialdehyde dehydrogenase.