GLUCONEOGENESIS (an energy-requiring pathway)

OVERVIEW
* tissues requiring constant supply of glucose => brain, RBCs, kidney medulla, lens and cornea of eye, testes, exercising muscle
* postprandial source of glucose for first 10-18 hours of fasting => liver glycogen (from glycogenolysis)
* during more prolonged fast => glucose formed from noncarbohydrate precursors such as lactate, pyruvate, glycerol (from lipolysis in adipocytes) and α-keto acids (from catabolism of glucogenic amino acids) = gluconeogenesis, which requires both mitochondrial and cytosolic enzymes
* during an overnight fast => 90% gluconeogenesis in liver and only 10% in kidney
* during more prolonged fast => 40% total glucose production by kidneys

SUBSTRATES FOR GLUCONEOGENESIS
* these are the molecules that can be used to produce a net synthesis of glucose
* gluconeogenic precursors => glycerol, lactate, α-keto acids,
* Alanine, a glucogenic amino acid, directly gives rise to pyruvate

A. Glycerol
* lipolysis in adipocytes --&gt; glycerol (in blood) --&gt; glycerol (in liver) --&gt; glycerol kinase --&gt; glycerol phosphate --&gt; glycerol phosphate dehydrogenase --&gt; DHAP
* adipocytes cannot phosphorylate glycerol because they essentially lack glycerol kinase

B. Lactate
* bloodborne glucose --&gt; RBCs/exercising skeletal muscles --&gt; lactate (in blood) --&gt; lactate (in liver) --&gt; reconverted to glucose (in liver) --&gt; glucose (in blood) = Cori cycle

C. Amino acids
* fasting --&gt; hydrolysis of proteins --&gt; glucogenic amino acids --&gt; α-keto acids (such as α-ketoglutarate) --&gt; enter Kreb’s cycle --&gt; formation of OAA (oxaloacetate, precursor of PEP)
* due to irreversible nature of pyruvate dehydrogenase, Acetyl CoA cannot be converted back to pyruvate, instead form ketone bodies
  acetoacetate, leucine, lysine

REACTIONS UNIQUE TO GLUCONEOGENESIS
* seven glycolytic reactions are reversible but the remaining three, irreversible reactions, are circumvented by four alternate reactions that energetically favor the synthesis of glucose

A. CARBOXYLATION OF PYRUVATE:
* pyruvate --&gt; pyruvate carboxylase --&gt; OAA --&gt; PEP-carboxykinase --&gt; PEP

B. TRANSPORT OF OAA TO THE CYTOSOL:
* OAA --&gt; mitochondrial malate dehydrogenase (MD) --&gt; malate (in mitochondria) --&gt; malate (in cytosol) --&gt; cytosolic malate dehydrogenase MD --&gt; OAA + NADH (this NADH is used in the reduction of 1,3-BPG to glyceraldehyde 3-phosphate)
* OAA can also be converted to aspartate, which is transported out of the mitochondria