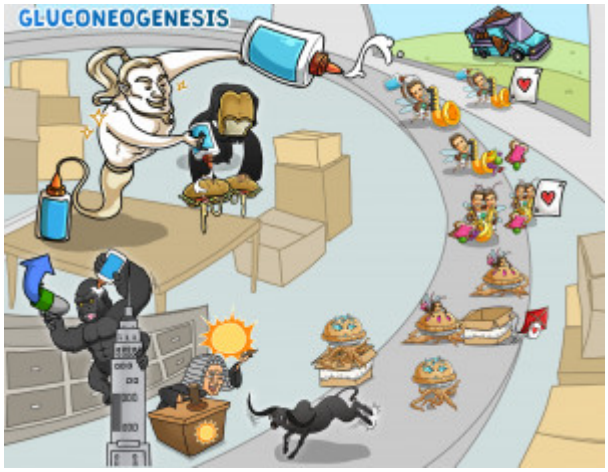
Gluconeogenesis

Gluconeogenesis is the process in which glucose is produced from non-carbohydrate substrates. This process is upregulated in times of fasting, which is signaled to our body by increased levels of glucagon, cortisol, and acetyl-CoA. The process begins in the mitochondria when pyruvate is converted into oxaloacetate by pyruvate carboxylase. Oxaloacetate is then shuttled out of the mitochondria and into the cytosol where it is converted into PEP by PEP carboxykinase. From PEP to fructose-1,6-bisphosphate, the pathway is identical to glycolysis. Once we reach fructose-1,6-bisphosphate, the enzyme fructose-1,6-bisphosphatase converts it into fructose-6-phosphate (contrast this with glycolysis in which phosphofructokinase converts fructose-6-phosphate into fructose-1,6-bisphosphate). Fructose-6-phosphate is then converted into glucose-6-phosphate, and then into glucose by tissues expressing the enzyme glucose-6-phosphatase. Tissues without this enzyme can convert glucose-6-phosphate into glycogen. Some patients' genes encode for defective glucose-6-phosphatase. These patients have glycogen storage disease type 1, or Von Gierke Disease. These patients present with massively increased glycogen stores and resulting hepatomegaly, hypoglycemia, ketosis, lactic acidosis, hyperuricemia and hyperlipidemia.



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OVERVIEW

Produces Glucose from Non-Carbohydrate Substrates

Glue from Nun-bread and Subs

During nighttime or prolonged fasts, there is less glucose readily available for the tissues of the body. However, the high-glucose requirements of certain tissues such as the brain and kidneys remains. To meet these requirements, the liver begins producing glucose from a variety of substrates. These include pyruvate (from glycolysis), lactate (from anaerobic metabolism), glycerol (from triglycerides), and various glucogenic amino acids.

Upregulated by Glucagon and Cortisol

Up-regulator by Glue-King-Kong and Court-of-Sol

Glucagon and cortisol are two hormones that act in opposition of insulin. When blood glucose is low, such as in fasting states, glucagon and cortisol are released from the pancreas and adrenal glands, respectively. These hormones signal tissues to begin synthesizing glucose so that it can be released into the blood for the rest of the body's tissues to use. Glucagon acts on G-protein receptors on hepatocytes, activating adenylate cyclase. Adenylate cyclase activates PKA, which then activates phosphorylase kinase. This activates glycogen phosphorylase, releasing stored glucose. PKA also phosphorylates pyruvate kinase, halting glycolysis.

PATHWAY

Pyruvate

Pie-with-Roots

The first step in gluconeogenesis requires pyruvate. This pyruvate can come from a variety of sources, namely the amino acids serine, threonine, glycine and cysteine. Some pyruvate can also come from stored glycogen.

Pyruvate Carboxylase

Pie-with-Roots Cardboard-box-lace

This mitochondrial enzyme is unique to gluconeogenesis, and is used to convert pyruvate into oxaloacetate. This enzyme requires CO_2, biotin, and energy in the form of ATP. Its activity is upregulated by acetyl-CoA.

Oxaloacetate

Ox

Oxaloacetate may be the second intermediary in gluconeogenesis, but it is the main fuel source for this pathway. Almost all glucogenic amino acids are converted into oxaloacetate before entering gluconeogenesis. In order to exit the mitochondria, oxaloacetate is temporarily converted to malate so that it can be transported via the malate-aspartate shuttle into the cytosol. Oxaloacetate is reconstituted in the cytosol.

Phosphoenolpyruvate (PEP) Carboxykinase

Fonz-Fairy-Eats-Pie-with-Roots and Cardboard-box-Kite-Ace

This cytosolic enzyme is responsible for the conversion of oxaloacetate to phosphoenolpyruvate, or PEP. It does this using GTP as a phosphate donor. Increased transcription of the PEPCK gene is mediated by glucagon and glucocorticoids.

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Phosphoenolpyruvate (PEP)

Fonz-Fairy-Eats-Pie-with-Roots

This gluconeogenic intermediary is the final product of the pathway used to bypass pyruvate kinase, and thus glycolysis. The formation of PEP constitutes one of the rate-limiting steps in gluconeogenesis.

Fructose-1,6-bisphosphate

Fruit-Toast mixed by (1) Wand in (6) Sax by 2 Fonz-Fairies

All of the steps and enzymes involved in gluconeogenesis from PEP to fructose-1,6-bisphosphate are identical to those in glycolysis. However, in order to bypass phosphofructokinase-1 (in glycolysis), the process of gluconeogenesis utilizes an alternative enzyme which is upregulated by citrate and downregulated by AMP and fructose-2,6 bisphosphate.

Fructose-1,6-bisphosphatase

Fruit-Toast mixed by (1) Wand in (6) Sax by 2 Fonz-Fairies-ace

This rate limiting enzyme is located in the cytosol. It is responsible for converting fructose-1,6,-bisphosphate to fructose-6-phosphate. Its activity is downregulated by AMP and fructose-2,6-phosphate, and upregulated by citrate.

Fructose-6-phosphate

Fruit-toast (6) Sax Fonz-fairy

This intermediary is common to both glycolysis and gluconeogenesis. It is important to note that dietary fructose enters the gluconeogenic pathway as fructose-1-phosphate, which is then converted into fructose-1,6-bisphosphate.

Glucose-6-phosphate

Glue-bottle (6) Sax Fonz-fairy

This molecule is the final intermediary in gluconeogenesis before we arrive at glucose. This molecule is only able to be converted into glucose by tissues with glucose 6-phosphatase activity, mainly the liver and kidneys. In tissues lacking this enzyme (like muscle), G6P is shunted towards glycogen formation.

Glucose 6-phosphatase

Glue-bottle (6) Sax Fonz-fairy-ace

This enzyme is located in the endoplasmic reticulum of the liver and kidneys, mainly. It converts glucose-6-phosphate to glucose, representing the final step in gluconeogenesis. In tissues with low or absent glucose 6-phosphatase activity (like skeletal muscle), excess glucose-6-phosphate is converted into glycogen. Von Gierke Disease is caused by a deficiency of this enzyme.

Glucose

Glue

Glucose is created as the last step and released into the bloodstream for use by other tissues by the liver and kidneys, mainly. Tissues that rely primarily on glucose for fuel include the eyes, RBCs, and the brain.

Clinical Relevance

Von Gierke Disease

Van Jerky

This disease represents a deficiency in the enzyme glucose 6-phosphatase. Since these patients are unable to convert glucose 6-phosphate into glucose, it is shunted towards glycogen formation. Patients present with massively increased glycogen stores and resulting hepatomegaly, hypoglycemia, ketosis, lactic acidosis, hyperuricemia and hyperlipidemia.

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