OBESITY

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WHAT IS THE OBESITY?

- Obesity is an excess of body fat that frequently results in a significant impairment of health.
- Doctors generally agree that men with more than 25% body fat and women with more than 30% are obese.
- Obesity is a known risk factor for chronic diseases including heart disease, diabetes, high blood pressure, stroke and some forms of cancer

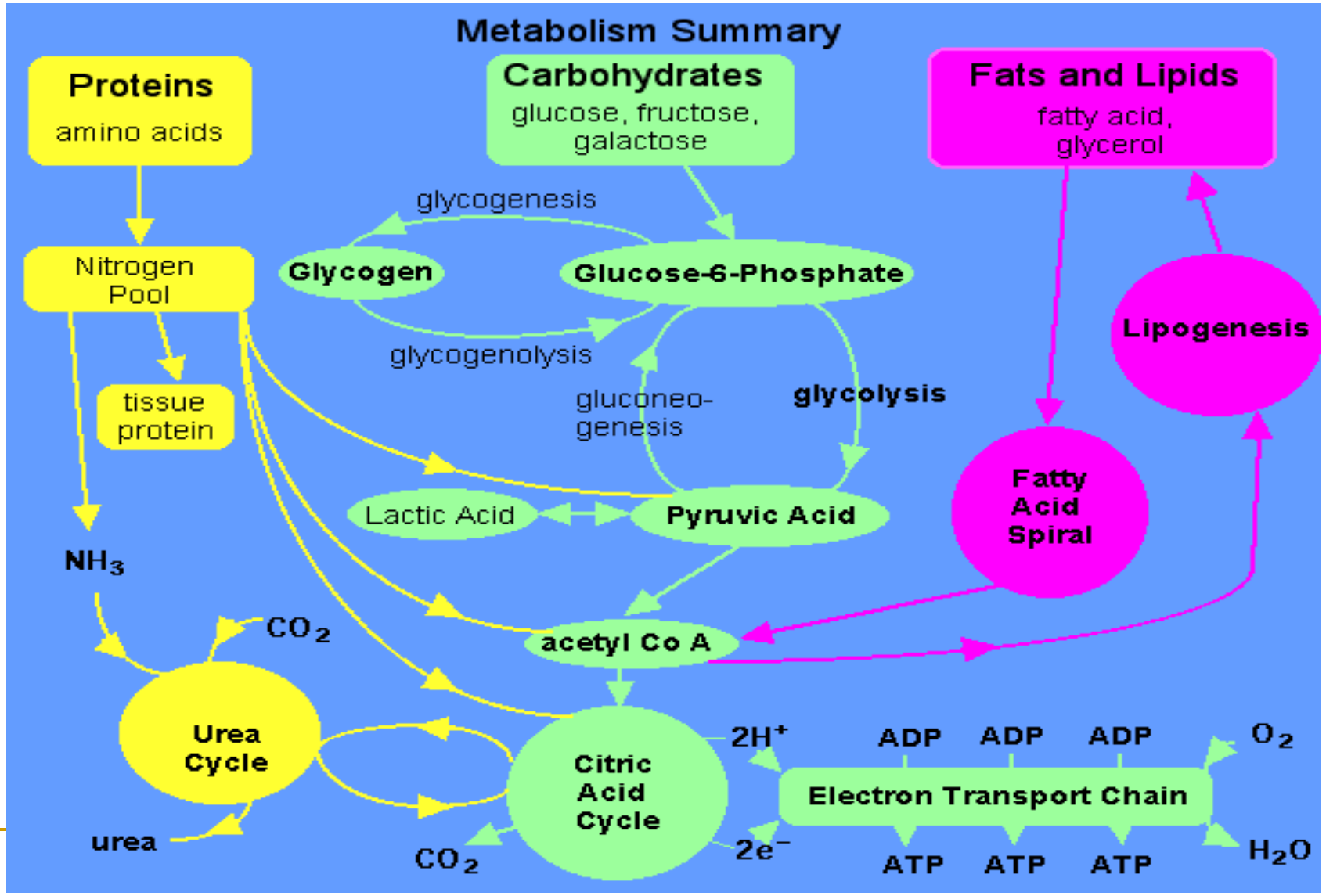
CAUSES OF OBESITY

- obesity is caused by consuming more calories than the body needs.

Most obesity is caused by energy imbalance – consuming more calories than the body expends

Other causes and contributing factors include:
- Environment
- Genetics
- Hormonal disorders
- Culture

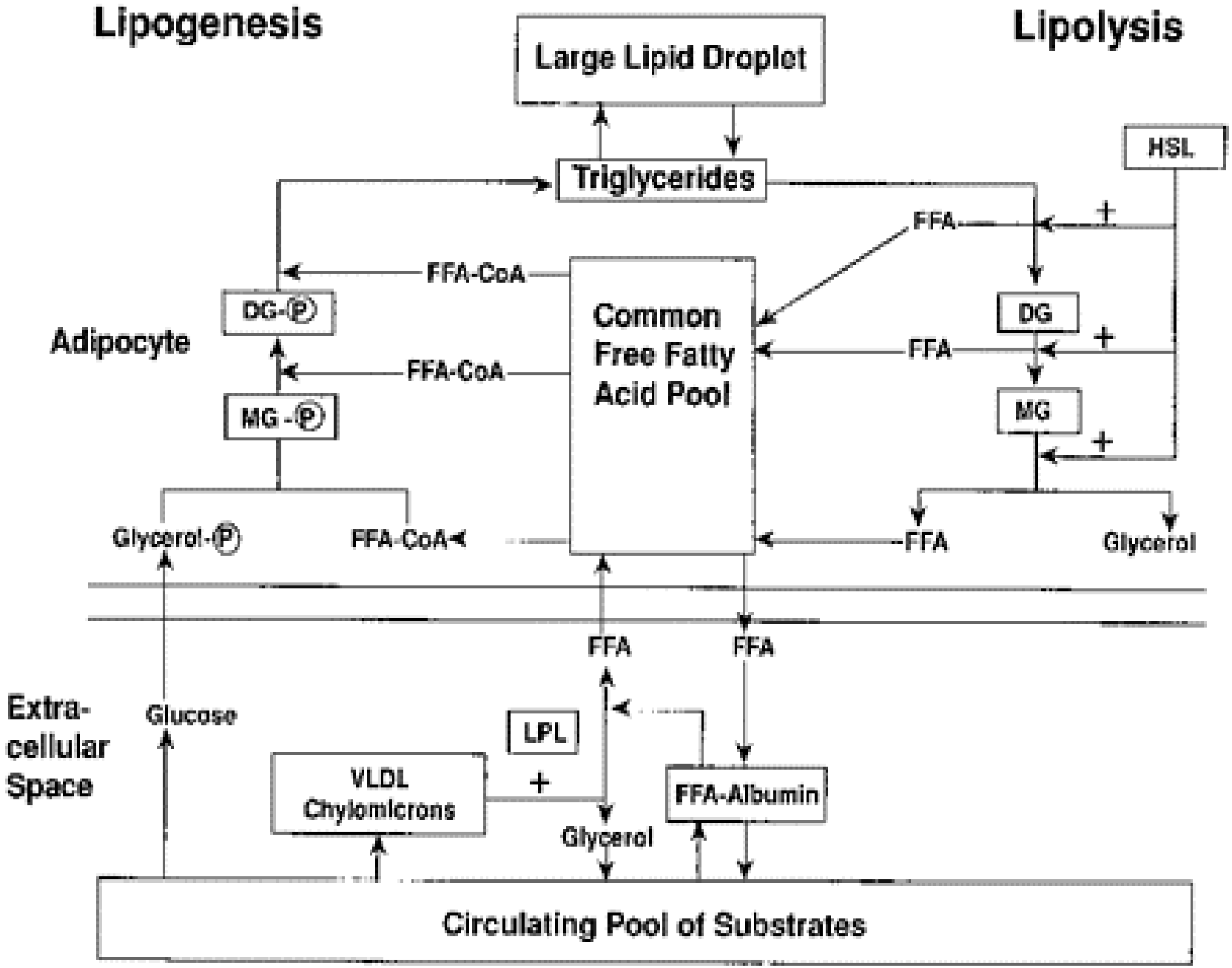
The relationships between lipid and carbohydrate metabolism are



- The first step in lipid metabolism is the hydrolysis of the lipid in the cytoplasm to produce glycerol and fatty acids.
- Since glycerol is a three carbon alcohol, it is metabolized quite readily into an intermediate in glycolysis, dihydroxyacetone phosphate

- The hydroxyacetone, obtained from glycerol is metabolized into one of two possible compounds. Dihydroxyacetone may be converted into pyruvic acid through the **glycolysis** pathway to make energy.
- In addition, the dihydroxyacetone may also be used in **gluconeogenesis** to make glucose-6-phosphate for glucose to the blood or glycogen depending upon what is required at that time

- Fatty acids are oxidized to acetyl CoA in the mitochondria using the fatty acid spiral. The acetyl CoA is then ultimately converted into ATP, CO_2, and H_2O using the citric acid cycle and the electron transport chain.
- Fatty acids are synthesized from carbohydrates and occasionally from proteins. Actually, the carbohydrates and proteins have first been catabolized into acetyl CoA. Depending upon the energy requirements, the acetyl CoA enters the citric acid cycle or is used to synthesize fatty acids in a process known as LIPOGENESIS


Lipogenesis
Lipolysis
Large Lipid Droplet
Triglycerides
HSL
FFA
FFA-CoA
DG-P
Adipocyte
Common Free Fatty Acid Pool
DG
FFA
FFA-CoA
MG-P
MG
Glycerol-P
FFA-CoA
FFA
Glycerol
FFA
FFA
Extra-cellular Space
Glucose
LPL
VLDL Chylomicrons
FFA-Albumin
Glycerol
Circulating Pool of Substrates

- Lipogenesis is the process by which glucose is converted to fatty acids.

- Lipogenesis is the deposition of fat. This process occurs in adipose tissue and in the liver at cytoplasmic and mitochondrial sites

- carbohydrate and protein consumed in the diet can be converted to fat

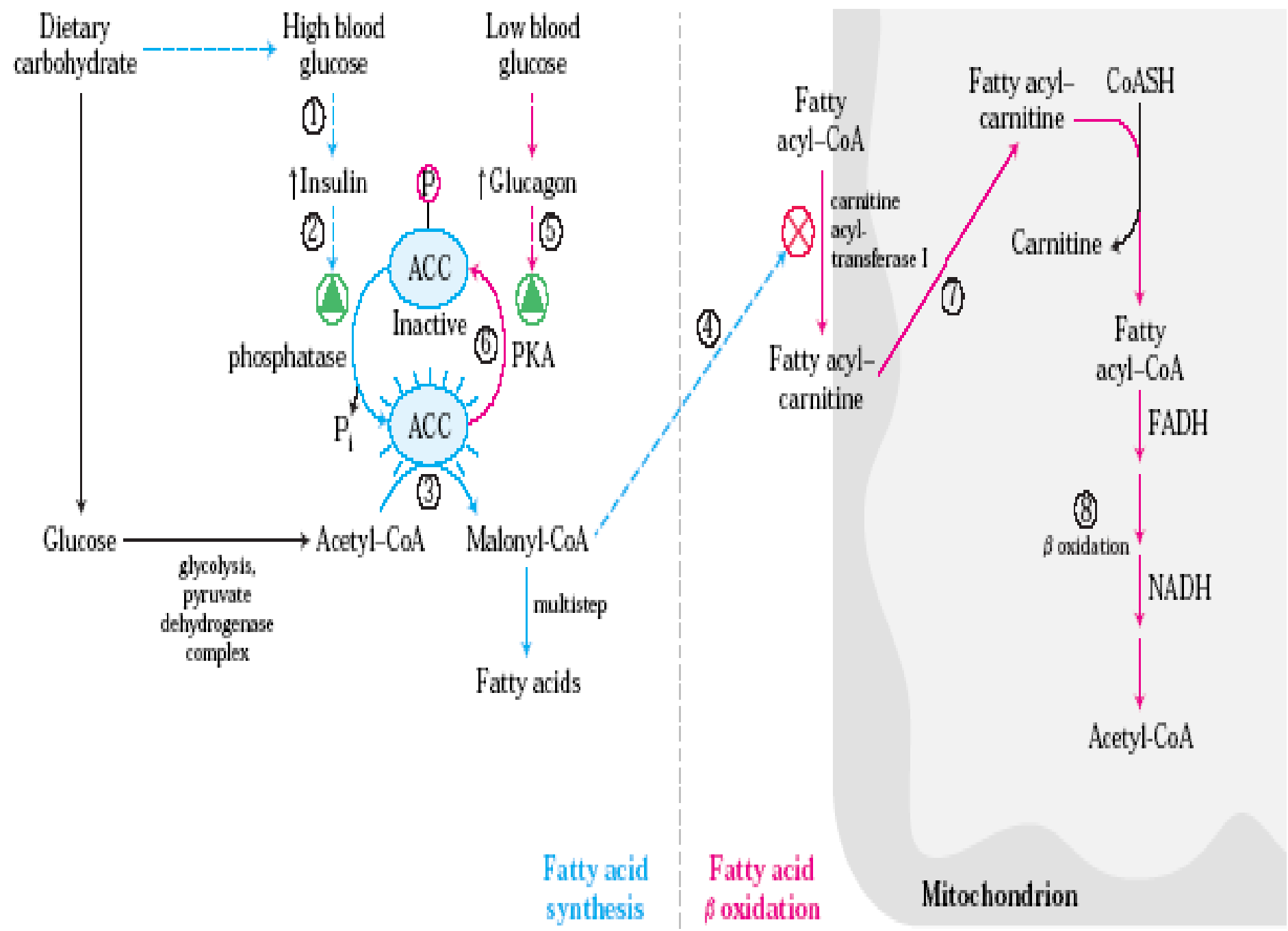
- Carbohydrate can also be converted to triglycerides primarily in the liver and transferred to adipose tissue for storage
- Amino acids from ingested proteins are used for new protein synthesis or they can be converted to carbohydrate and fat.

- Fatty acids, in the form of triglycerides or free fatty acids bound to albumin, are ingested in the diet or synthesized by the liver
- Very little synthesis of free fatty acids occurs in the adipocytes. Triglycerides are the most significant source of fatty acids, because this is the form in which dietary lipids are assembled by the gut and liver

- Triglycerides made up of long chain fatty acids, in the form of chylomicrons (from intestinal absorption) or lipoproteins (from hepatic synthesis), are hydrolyzed to glycerol and free fatty acids by an enzyme called lipoprotein lipase (LPL). Lipoprotein lipase is synthesized in adipocytes and secreted into adjacent endothelial cells.

- . Fatty acids that are stored in the adipose tissue must first combine with coenzyme A to form a thioester and then they are re-esterified in a stepwise manner to triglycerides.
- Glucose is the primary source of glycerol for this re-esterification process.
- Only a small amount of glycerol released, when triglycerides are hydrolyzed by LPL, can be reused by adipocytes to form alpha glycerol phosphate to be used for trigyceride assembly. Most glycerol is returned to the circulation.

- Lipolysis is the chemical decomposition and release of fat from adipose tissue. This process predominates over lipogenesis when additional energy is required
- The triglycerides within the adipocyte are acted upon by a multi-enzyme complex called hormone sensitive lipase (HSL), which hydrolyzes the triglyceride into free fatty acids and glycerol. These lipases act consecutively on triglycerides, diglycerides, and monoglycerides. Triglyceride lipase regulates the rate of lipolysis, because its activity is low


Dietary carbohydrate
High blood glucose
Low blood glucose
1
↑Insulin
↑Glucagon
2
5
P
ACC
Inactive
phosphatase
6
PKA
P_i
ACC
3
Glucose
glycolysis, pyruvate dehydrogenase complex
Acetyl-CoA
Malonyl-CoA
multistep
Fatty acids
4
Fatty acyl-CoA
carnitine acyl-transferase I
Fatty acyl-carnitine
7
Fatty acyl-carnitine
CoASH
Carnitine
Fatty acyl-CoA
FADH
8
β oxidation
NADH
Acetyl-CoA
Fatty acid synthesis
Fatty acid β oxidation
Mitochondrion

- Insulin is an indicator of the blood sugar level of the body, Insulin stimulates lipogenesis in three main ways.

- **Malonyl-coenzyme A**
- In fat synthesis, the enzyme pyruvate dehydrogenase, which forms acetyl-coA, and also acetyl-coA carboxylase which forms malonyl-coA are obvious control points. These are activated by insulin.
- This leads to an overall increase in the levels of malonyl-coenzyme A, which is the substrate required for fat synthesis.
- **Pyruvate dehydrogenase dephosphorylation**
- Pyruvate dehyrdrogenase dephosphorylation is increased with the release of insulin.
- The dephosphorylated form is more active.

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- **Acetyl-coA carboxylase**
- Insulin affects ACC in a similar way to PDH.
- It leads to its dephosphorylation.
- Glucagon has an antagonistic effect and increases phosphorylation, therefore inhibiting ACC, and slowing fat synthesis. This inhibition mechanism is thought to be something to do with ACC-dependent protein kinase.
- Affecting ACC affects the rate of acetyl-coA conversion to malonyl-coA. Malonyl-coA increae pushes the equilibrium over to increase production of fatty acids through biosynthesis.
- AMP activated protein kinase acts as a measure of the ATP needs of a cell and acts to phosphorylse ACC. When ATP is depleted there is a rise in 5'AMP. This rise activates AMP-activated protein kinase, which phosphorylates ACC and thereby inhibits fat synthesis. This is a useful way to ensure that glucose is not diverted down a storage pathway in times when energy levels are low.

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