Triacylglyceride Metabolism

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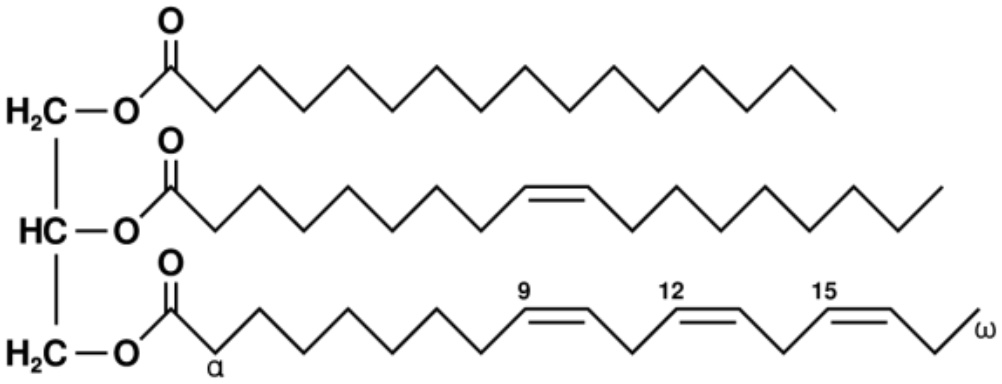
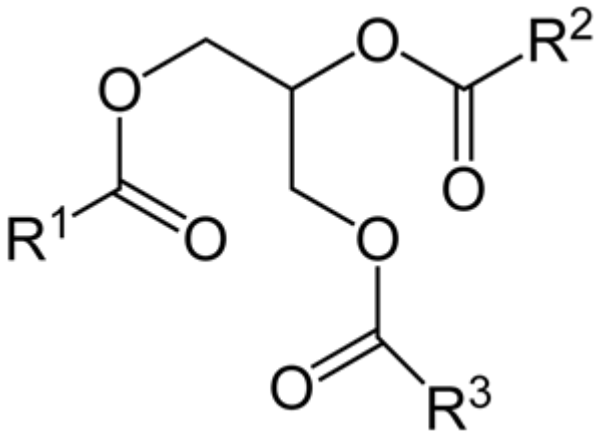
Triacylglycerides are a group of insoluble compounds that serve as energy reserves in the body. Their storage occurs in adipocytes, which are built up or depleted in response to the constantly changing energy demands of the cell. Both of these processes are under tight hormonal regulation. This discussion will also include the absorption and transport of fatty acids, as well as the production of ketone bodies.



Triacylglyceride Structure



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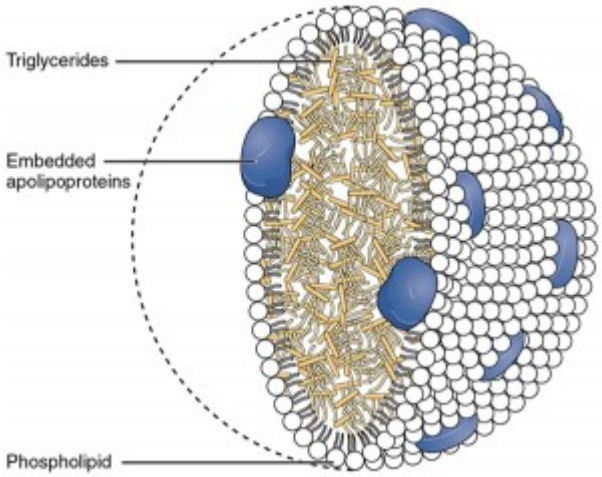
Triacylglycerides possess a glycerol backbone, derived from either glyceraldehyde-3-phosphate or dihydroxyacetone phosphate produced in glycolysis. Esterified to the glycerol backbone are three fatty acid chains, which consist of nonpolar hydrocarbon tails that vary in their length as well as the degree of saturation. Free fatty acids possess a terminal carboxylate group (-COO^-), which has a high affinity for water. This feature

makes fatty acids amphiphilic molecules. Long-chain fatty acids are insoluble in water and must be transported along with albumin.

90 % of fatty acids are found in plasma esterified (as triacylglycerol, phospholipids, or cholesteryl esters) and conjugated to circulating lipoproteins.



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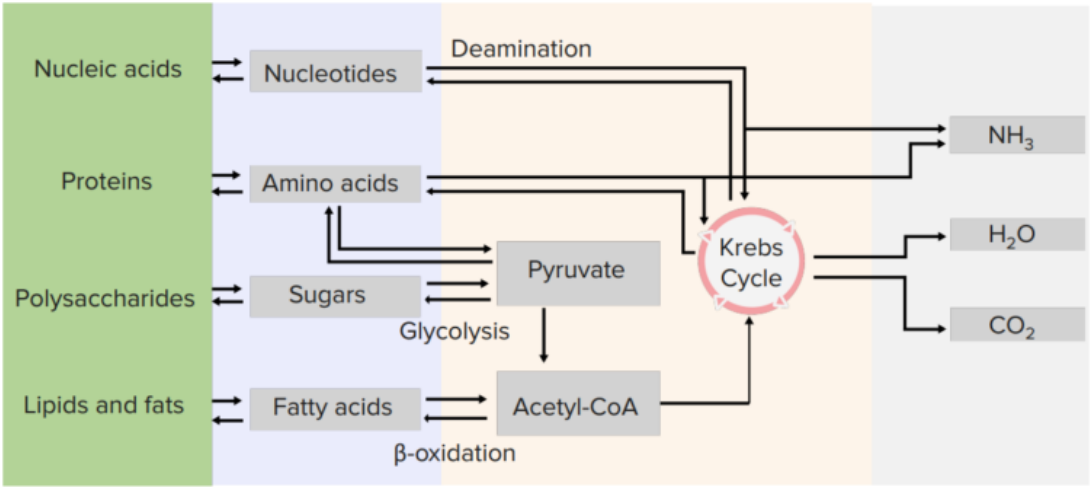
Macromolecule Building Blocks



A review of the macromolecular building blocks and where they fit into cellular respiration.

Fatty Acid Synthesis

The diet supplies the body with the majority of the fatty acids it needs. Excess carbohydrates and amino acids are converted to fatty acids, which are stored as triacylglycerides. Fatty acid takes place in the liver and adipose tissue, and in mammary glands of lactating mothers.

Fatty acid synthesis takes place in the cytosol after acetyl-CoA is brought from the mitochondria via the **tricarboxylate transport system** and activated to malonyl-CoA by **acetyl-CoA carboxylase (ACC)**. This must happen because the CoA portion of

acetyl-CoA cannot cross the inner mitochondrial membrane, only the acetyl portion can. The acetyl unit crosses into the cytosol as part of the citrate produced by the condensation of oxaloacetate and acetyl-CoA. The subsequent acetyl-CoA carboxylase reaction requires CO_2 and ATP, the former being provided by biotin covalently bound to the enzyme.

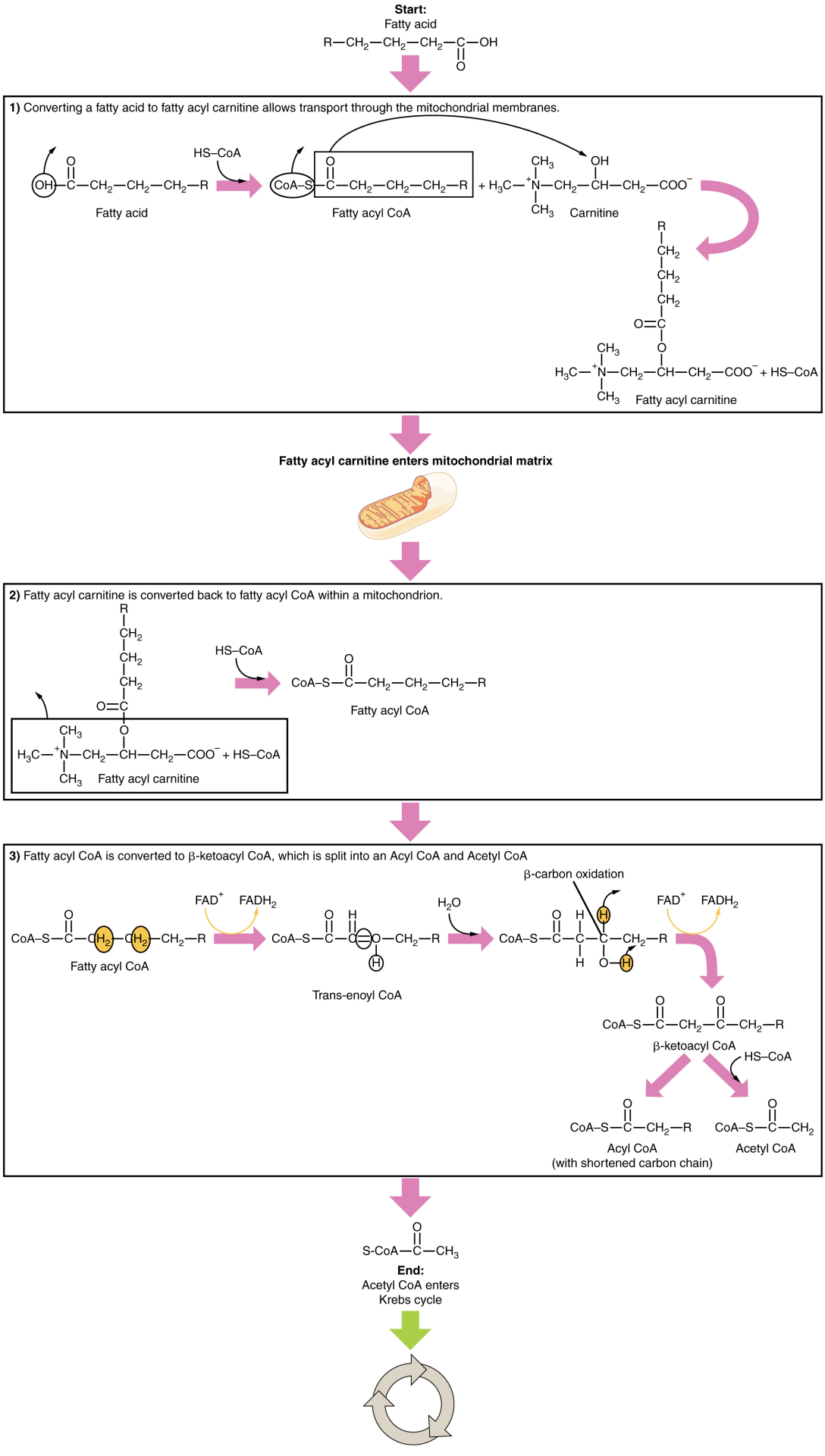
Fatty acid synthase (FAS) is a multifunctional homodimer that catalyzes a series of seven reactions that extend acyl-ACP units by two at a time. The first of FAS' enzymatic activities condenses the acyl group with malonyl-ACP to form a ketoacyl intermediate. Next, FAS produces an acyl-ACP molecule by using two reductions and a dehydration reaction that all resemble effectively the reverse of β-Oxidation. After seven reaction cycles of extending acyl-ACP units two at a time, Palmitate (C_{16}) is produced and is cleaved from ACP by **thioesterase**.

From Palmitate other fatty acids are synthesized by the employment of **elongases and desaturases**, which extend the fatty acid chain and generate double bonds. It is worth note that human triacylglycerides synthesized from fatty acyl-CoA and glyceraldehyde-3-phosphate or dihydroxyacetone phosphate typically contain saturated fatty acids at carbon 1 and unsaturated fatty acids at carbon 2 of the glycerol backbone.

For those who prefer to understand the reactions of fatty acid synthesis as a series of seven different step-wise enzymatic activities, one can name the pathway as follows.

Acetyl-CoA-ACP acetyl transacylase transfers a molecule of acetate from acetyl-CoA to the thiol group of the ACP domain in step one. **Malonyl-CoA-ACP transacylase** next accepts a three-carbon malonate unit from malonyl-CoA, and a four-carbon is attached to the ACP domain as the acetyl-group condenses with the malonyl group on ACP. In this third step catalyzed by **3-ketoacyl-ACP**, the CO_2 added by ACC is released, proving the energy for the reaction.

The 3-ketoacyl groups are conveyed onto the saturated acyl group via a pair of reductive steps that require NADPH and dehydration. Step four is the **3-ketoacyl-ACP reductase** step, which produces alcohol, and a water molecule is removed in the introduction of a double bond between carbons 2 & 3 by **3-Hydroxyacyl-ACP dehydratase** in step 5. Step six is performed by **Enoyl-ACP reductase**, which reduces the double bond.



Fat Mobilization

Triacylglyceride digestion depends on bile acids' emulsifying capabilities as well as the activation of **lipases** function at the lipid-water interface. Lipoproteins, which are complexes of hydrophobic lipids coated with amphipathic lipids and apolipoproteins, convey lipids through the circulatory system. LDL is then taken up via receptor-mediated endocytosis, which allows cells to take in cholesterol and other lipids for use.

Mobilization of stored fat in adipose tissue requires the release of free fatty acids from the glycerol backbone of the triacylglyceride, accomplished by **Hormone-sensitive lipase (HSL)**. This enzyme removes fatty acid chains from the 1 or 3 positions of the glycerol backbone, and other specific lipases finish off the process by handling diacylglycerols and monoacylglycerols. HSL is activated when it is in the phosphorylated form, a process that occurs through cAMP-dependent protein kinases in response to epinephrine or glucagon.

The glycerol backbone that remains cannot be metabolized by adipose tissue, and instead, it is transported to the liver. Here, glycerol is phosphorylated by **glycerol kinase** to form glycerol-3-phosphate, which can be converted to dihydroxyacetone phosphate in a direct reversal of the glycerol-3-phosphate dehydrogenase reaction. These two compounds can enter flux through the glycolytic or gluconeogenic pathways.

Free fatty acids cleaved from the glycerol backbone diffuse through the lipid bilayer and bind to albumin, where they can be transported to other tissues and be activated to their CoA derivatives or oxidized to produce cellular energy.

β-Oxidation

β-Oxidation is the process by which fatty acids are broken down, and it begins with the activation of the acyl group by the formation of a thioester bond to CoA. This acyl group is carried by carnitine into the mitochondria from the cytosol by use of the **carnitine shuttle**. Inside the mitochondria, the acyl group is re-esterified to CoA.

β-Oxidation proceeds in a series of four reactions that

1. form a double bond
2. hydrate the double bond
3. form a **β-ketoacyl-CoA** via dehydrogenation
4. produce acetyl-CoA and an acyl-CoA shortened by two carbons via thiolysis.

This process is repeated until fatty acids with an even number of carbon atoms are all converted to acetyl-CoA, or fatty acids with odd numbers of carbon atoms are converted to acetyl-CoA and one propionyl-CoA. Acetyl-CoA enters the TCA cycle by condensing with oxaloacetate, and propionyl-CoA is converted to succinyl-CoA, and both are eventually oxidized to generate ATP. Also produced in β-oxidation are FADH2 and NADH.

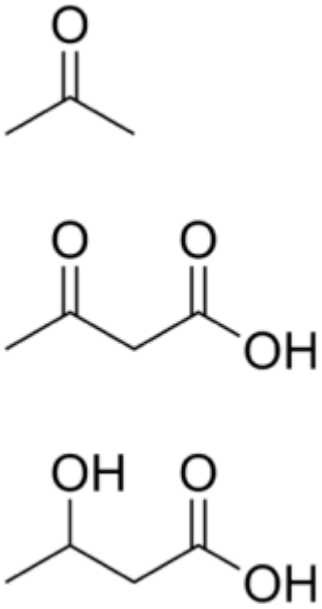
Unsaturated fatty acids require isomerases to convert their Δ^3 double bonds to Δ^2 double bonds, as well as reductases to remove Δ^4 double bonds. Very long fatty acids are first partially oxidized in peroxisomes by a three-enzyme system.

The energy produced from the complete β-oxidation of one fatty acid is high. Palmitate, for example, produces a net of 129 ATP from its complete oxidation to CO_2 and H_2O. This number comes from the 8 acetyl-CoA, 7 NADH, and 7 $FADH_2$ formed, along with the two ATP that is required in the activation of the fatty acid.

Ketone Body Metabolism

The liver produces **acetoacetate** and **β-hydroxybutyrate** from acetyl-CoA. These are also known as **ketone bodies**, and they are released into the bloodstream to tissues, which can use them for fuel by converting them back to acetyl-CoA, which is oxidized by the TCA cycle. Because ketone bodies do not need to be incorporated into albumin or lipoproteins to be transported, they serve as an important source of carbon skeletons in energy metabolism for peripheral tissues.

Note: The brain also uses ketone bodies as a source of energy when the concentration of blood glucose is low, such as the scenario that plays out during prolonged fasting or starvation.



Chemical structures of various ketone bodies – acetone, acetoacetic acid, and beta-hydroxybutyric acid.

Ketone body biosynthesis proceeds when fatty acids mobilized from adipose tissue flood the liver, eventually elevating the hepatic concentration of acetyl-CoA. The resulting excess of acetyl-CoA has a **dual effect on metabolism**; it inhibits pyruvate dehydrogenase and activates pyruvate carboxylase, which would push the flux of substrates toward gluconeogenesis. The reason this does not occur is that oxidation of fatty acids produces an excess of NADH, which inhibits malate dehydrogenase. The overall consequence of this is that acetyl-CoA is fluxed away from gluconeogenesis, away from the TCA cycle, and into ketone body synthesis.

Acetyl-CoA is first converted to acetoacetyl-CoA and then to HMG-CoA by two enzymes, **thiolase** and **HMG-CoA synthase (HMGCS)**. This is the same pathway that occurs in cholesterol biosynthesis. However, instead of generating mevalonate by using **HMG-CoA reductase (HMGCR)**, the cell uses **HMG-CoA lyase (HMGCL)** to produce acetoacetate. β-hydroxybutyrate and acetone can now be formed by the actions of their respective forming enzymes **β-hydroxybutyrate dehydrogenase** and **acetoacetate decarboxylase**, respectively.

Regulation of Fatty Acid Metabolism

Both β-oxidation and fatty acid synthesis are hormonally regulated. **Glucagon** and epinephrine activate hormone-sensitive lipase in adipose tissue, thereby increasing the concentration of fatty acids for oxidation, as well as inactivating acetyl-CoA carboxylase. This works to shut off fat synthesis because ACC is the rate-limited and regulated step of the pathway. Secondarily, **AMP-activated protein kinase (AMPK)** phosphorylates ACC to inactivate the enzyme when it is itself phosphorylated by cAMP-dependent protein kinase A.

Insulin works to oppose the actions of glucagon and epinephrine, by first up-regulating the amount of acetyl-CoA carboxylase synthesis for the production of fatty acids, and by up-regulating the synthesis of fatty acid synthase. Insulin also causes ACC to be dephosphorylated by phosphatases, which activate the enzyme. Allosterically, citrate activates ACC, which "tells" the cell that there are plenty of substrates available for energy production and excess carbon should be fluxed towards energy storage.

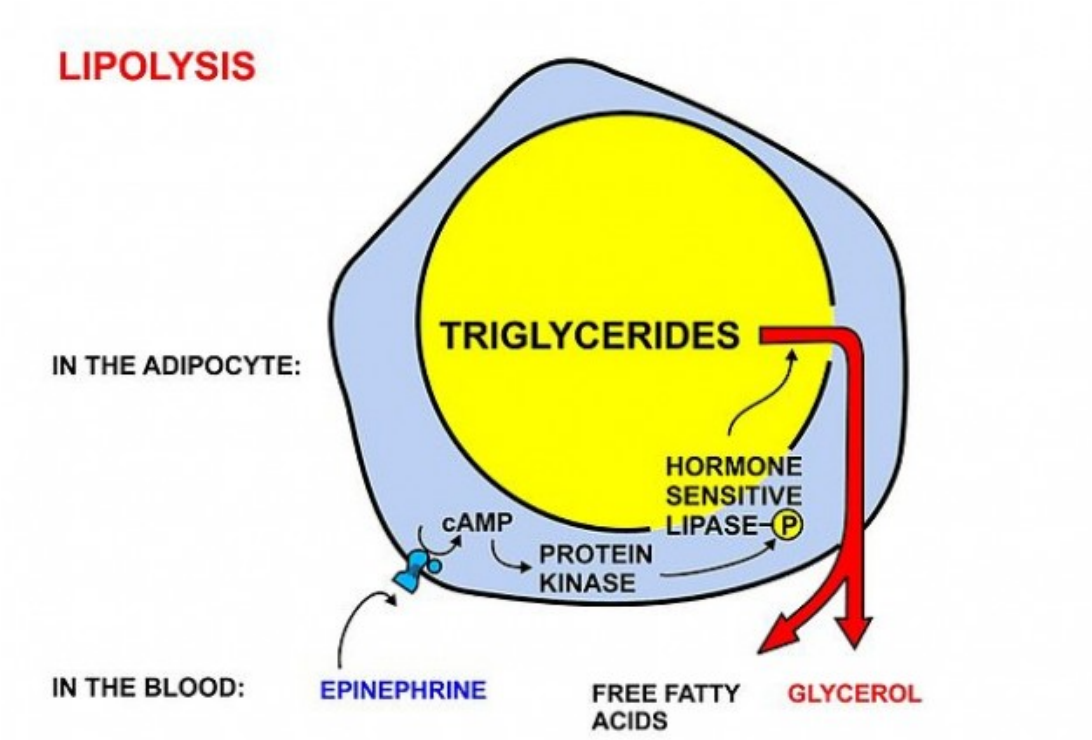


Image: "A diagrammatic illustration of the process of lipolysis (in a fat cell) induced by high epinephrine and low insulin levels in the blood. Free fatty acids and glycerol are released into the blood." by Cruithne9. License: CC BY-SA 4.0

In the long term, the production of ACC and FAS are controlled by transcriptional regulation. In the fed state of metabolism, prolonged exposure to glucose stimulates **Sterol regulatory element-binding protein (SREBP)** to translocate to the nucleus where it binds the **sterol regulatory element (SRE)**. This increases the rate of ACC and FAS transcription. Conversely, SREBP can be prevented from translocating to the nucleus and binding to SRE, which will cause the production of these enzymes to be attenuated.

The **carnitine shuttle** can also be regulated in response to the changing needs of the cell. Malonyl-CoA inhibits the entry of acyl groups into the mitochondrial matrix, thereby preventing any newly formed fatty acids from being degraded. Fatty acid oxidation is also regulated by the ratio of acetyl-CoA to CoA ratio. When the ratio increases, the CoA-

requiring thiolase of oxidation is inhibited.

References

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Notes