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MATRIC NO; 18/mhs02/147

COURSE; BIOCHEMISTRY

ASSIGNMENT

Describe the three stages of beta oxidation. Show pathways where necessary.

 **beta-oxidation** is the [catabolic process](https://en.wikipedia.org/wiki/Catabolism) by which [fatty acid](https://en.wikipedia.org/wiki/Fatty_acid) molecules are broken down[[1]](https://en.wikipedia.org/wiki/Beta_oxidation#cite_note-1) in the cytosol in prokaryotes and in the [mitochondria](https://en.wikipedia.org/wiki/Mitochondria) in eukaryotes to generate [acetyl-CoA](https://en.wikipedia.org/wiki/Acetyl-CoA), which enters the [citric acid cycle](https://en.wikipedia.org/wiki/Citric_acid_cycle), and [NADH](https://en.wikipedia.org/wiki/NADH) and [FADH2](https://en.wikipedia.org/wiki/FADH2), which are co-enzymes used in the [electron transport chain](https://en.wikipedia.org/wiki/Electron_transport_chain). It is named as such because the [beta carbon](https://en.wikipedia.org/wiki/Alpha_and_beta_carbon) of the fatty acid undergoes oxidation to a [carbonyl](https://en.wikipedia.org/wiki/Carbonyl) group. Beta-oxidation is primarily facilitated by the [mitochondrial trifunctional protein](https://en.wikipedia.org/wiki/Mitochondrial_trifunctional_protein), an enzyme complex associated with the [inner mitochondrial membrane](https://en.wikipedia.org/wiki/Inner_mitochondrial_membrane), although [very long chain fatty acids](https://en.wikipedia.org/wiki/Very_long_chain_fatty_acid) are oxidized in [peroxisomes](https://en.wikipedia.org/wiki/Peroxisome).

The overall reaction for one cycle of beta oxidation is:

C*n*-acyl-CoA + FAD + NAD+
+ H
2O + CoA → C*n*-2-acyl-CoA + FADH
2 + NADH + H+
+ acetyl-CoA



**Activation and membrane transport**

Free fatty acids cannot penetrate any biological membrane due to their negative charge. Free fatty acids must cross the cell membrane through specific [transport proteins](https://en.wikipedia.org/wiki/Transport_proteins), such as the [SLC27](https://en.wikipedia.org/wiki/Solute_carrier_family) family fatty acid transport protein.Once in the [cytosol](https://en.wikipedia.org/wiki/Cytosol), the following processes bring fatty acids into the mitochondrial matrix so that beta-oxidation can take place.

1. [Long-chain-fatty-acid—CoA ligase](https://en.wikipedia.org/wiki/Long-chain-fatty-acid%E2%80%94CoA_ligase) catalyzes the reaction between a fatty acid with [ATP](https://en.wikipedia.org/wiki/Adenosine_triphosphate) to give a fatty acyl adenylate, plus inorganic pyrophosphate, which then reacts with free [coenzyme A](https://en.wikipedia.org/wiki/Coenzyme_A) to give a fatty acyl-CoA ester and [AMP](https://en.wikipedia.org/wiki/Adenosine_monophosphate).
2. If the fatty acyl-CoA has a long chain, then the [carnitine shuttle](https://en.wikipedia.org/wiki/Carnitine#Carnitine_shuttle:_Activation_and_transportation_of_fatty_acids_into_the_mitochondria) must be utilized:
	1. Acyl-CoA is transferred to the hydroxyl group of carnitine by [carnitine palmitoyltransferase I](https://en.wikipedia.org/wiki/Carnitine_palmitoyltransferase_I), located on the cytosolic faces of the [outer](https://en.wikipedia.org/wiki/Outer_mitochondrial_membrane) and [inner mitochondrial membranes](https://en.wikipedia.org/wiki/Inner_mitochondrial_membrane).
	2. Acyl-carnitine is shuttled inside by a [carnitine-acylcarnitine translocase](https://en.wikipedia.org/wiki/Carnitine-acylcarnitine_translocase), as a carnitine is shuttled outside.
	3. Acyl-carnitine is converted back to acyl-CoA by [carnitine palmitoyltransferase II](https://en.wikipedia.org/wiki/Carnitine_palmitoyltransferase_II), located on the interior face of the [inner mitochondrial membrane](https://en.wikipedia.org/wiki/Inner_mitochondrial_membrane). The liberated carnitine is shuttled back to the cytosol, as an acyl-carnitine is shuttled into the matrix.
3. If the fatty acyl-CoA contains a short chain, these [short-chain fatty acids](https://en.wikipedia.org/wiki/Short-chain_fatty_acid) can simply diffuse through the inner mitochondrial membrane.[[4]](https://en.wikipedia.org/wiki/Beta_oxidation#cite_note-4)

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**General mechanism**

Once the fatty acid is inside the [mitochondrial matrix](https://en.wikipedia.org/wiki/Mitochondrial_matrix), beta-oxidation occurs by cleaving two carbons every cycle to form acetyl-CoA. The process consists of 4 steps.

1. A long-chain fatty acid is [dehydrogenated](https://en.wikipedia.org/wiki/Dehydrogenation) to create a trans [double bond](https://en.wikipedia.org/wiki/Double_bond) between C2 and C3. This is catalyzed by [acyl CoA dehydrogenase](https://en.wikipedia.org/wiki/Acyl_CoA_dehydrogenase) to produce trans-delta 2-enoyl CoA. It uses FAD as an electron acceptor and it is reduced to FADH2.
2. Trans-delta2-enoyl CoA is hydrated at the double bond to produce L-3-hydroxyacyl CoA by [enoyl-CoA hydratase](https://en.wikipedia.org/wiki/Enoyl-CoA_hydratase).
3. L-3-hydroxyacyl CoA is dehydrogenated again to create 3-ketoacyl CoA by 3-hydroxyacyl CoA dehydrogenase. This enzyme uses NAD as an electron acceptor.
4. [Thiolysis](https://en.wikipedia.org/wiki/Thiolysis) occurs between C2 and C3 (alpha and beta carbons) of 3-ketoacyl CoA. Thiolase enzyme catalyzes the reaction when a new molecule of coenzyme A breaks the bond by nucleophilic attack on C3. This releases the first two carbon units, as acetyl CoA, and a fatty acyl CoA minus two carbons. The process continues until all of the carbons in the fatty acid are turned into acetyl CoA.

Fatty acids are oxidized by most of the tissues in the body. However, some tissues such as the [red blood cells](https://en.wikipedia.org/wiki/Erythrocytes) of mammals (which do not contain mitochondria),and cells of the [central nervous system](https://en.wikipedia.org/wiki/Central_nervous_system) do not use fatty acids for their energy requirements,[[6]](https://en.wikipedia.org/wiki/Beta_oxidation#cite_note-:0-6) but instead use carbohydrates (red blood cells and neurons) or [ketone bodies](https://en.wikipedia.org/wiki/Ketone_bodies) (neurons only).

Because many fatty acids are not fully saturated or do not have an even number of carbons, several different mechanisms have evolved, described below.

**Even-numbered saturated fatty acids**

Once inside the mitochondria, each cycle of β-oxidation, liberating a two carbon unit ([acetyl-CoA](https://en.wikipedia.org/wiki/Acetyl-CoA)), occurs in a sequence of four reactions:

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| --- | --- | --- | --- |
| **Description** | **Diagram** | **Enzyme** | **End product**  |
| [*Dehydrogenation*](https://en.wikipedia.org/wiki/Dehydrogenation) *by* [*FAD*](https://en.wikipedia.org/wiki/Flavin_adenine_dinucleotide)*:* The first step is the oxidation of the fatty acid by Acyl-CoA-Dehydrogenase. The enzyme catalyzes the formation of a [double bond](https://en.wikipedia.org/wiki/Double_bond) between the C-2 and C-3. | Beta-Oxidation1.svg | [acyl CoA dehydrogenase](https://en.wikipedia.org/wiki/Acyl_CoA_dehydrogenase) | trans-Δ2-enoyl-CoA  |
| *Hydration:* The next step is the [hydration](https://en.wikipedia.org/wiki/Hydration_reaction) of the bond between C-2 and C-3. The reaction is [stereospecific](https://en.wikipedia.org/wiki/Stereospecific), forming only the L [isomer](https://en.wikipedia.org/wiki/Isomer). | Beta-Oxidation2.svg | [enoyl CoA hydratase](https://en.wikipedia.org/wiki/Enoyl_CoA_hydratase) | L-β-hydroxyacyl CoA  |
| [*Oxidation*](https://en.wikipedia.org/wiki/Oxidation) *by* [*NAD+*](https://en.wikipedia.org/wiki/NADH)*:* The third step is the [oxidation](https://en.wikipedia.org/wiki/Oxidation) of L-β-hydroxyacyl CoA by NAD+. This converts the [hydroxyl](https://en.wikipedia.org/wiki/Hydroxyl) group into a [keto](https://en.wikipedia.org/wiki/Ketone) group. | Beta-Oxidation3.svg | [3-hydroxyacyl-CoA dehydrogenase](https://en.wikipedia.org/wiki/3-hydroxyacyl-CoA_dehydrogenase) | β-ketoacyl CoA  |
| [*Thiolysis*](https://en.wikipedia.org/wiki/Thiolysis)*:* The final step is the cleavage of β-ketoacyl CoA by the [thiol](https://en.wikipedia.org/wiki/Thiol) group of another molecule of [Coenzyme A](https://en.wikipedia.org/wiki/Coenzyme_A). The thiol is inserted between C-2 and C-3. | Beta-Oxidation4.svg | [β-ketothiolase](https://en.wikipedia.org/wiki/%CE%92-ketothiolase) | An [acetyl-CoA](https://en.wikipedia.org/wiki/Acetyl-CoA) molecule, and an [acyl-CoA](https://en.wikipedia.org/wiki/Acyl-CoA) molecule that is two carbons shorter  |

This process continues until the entire chain is cleaved into acetyl CoA units. The final cycle produces two separate acetyl CoAs, instead of one acyl CoA and one acetyl CoA. For every cycle, the Acyl CoA unit is shortened by two carbon atoms. Concomitantly, one molecule of FADH2, NADH and acetyl CoA are formed.

**Odd-numbered saturated fatty acid**

In general, fatty acids with an odd number of carbons are found in the lipids of plants and some marine organisms. Many ruminant animals form a large amount of 3-carbon propionate during the fermentation of carbohydrates in the rumen.[[8]](https://en.wikipedia.org/wiki/Beta_oxidation#cite_note-8) Long-chain fatty acids with an odd number of carbon atoms are found particularly in ruminant fat and milk.[[9]](https://en.wikipedia.org/wiki/Beta_oxidation#cite_note-9)

Chains with an odd-number of [carbons](https://en.wikipedia.org/wiki/Carbon) are oxidized in the same manner as even-numbered chains, but the final products are [propionyl-CoA](https://en.wikipedia.org/wiki/Propionyl-CoA) and Acetyl CoA

Propionyl-CoA is first carboxylated using a [bicarbonate](https://en.wikipedia.org/wiki/Bicarbonate) [ion](https://en.wikipedia.org/wiki/Ion) into D-stereoisomer of methylmalonyl-CoA, in a reaction that involves a [biotin](https://en.wikipedia.org/wiki/Biotin) [co-factor](https://en.wikipedia.org/wiki/Cofactor_%28biochemistry%29), ATP, and the enzyme [propionyl-CoA carboxylase](https://en.wikipedia.org/wiki/Propionyl-CoA_carboxylase). The bicarbonate ion's carbon is added to the middle carbon of propionyl-CoA, forming a D-methylmalonyl-CoA. However, the D conformation is enzymatically converted into the L conformation by [methylmalonyl-CoA epimerase](https://en.wikipedia.org/wiki/Methylmalonyl-CoA_epimerase), then it undergoes intramolecular rearrangement, which is catalyzed by [methylmalonyl-CoA mutase](https://en.wikipedia.org/wiki/Methylmalonyl-CoA_mutase) (requiring B12 as a coenzyme) to form succinyl-CoA. The [succinyl-CoA](https://en.wikipedia.org/wiki/Succinyl-CoA) formed can then enter the [citric acid cycle](https://en.wikipedia.org/wiki/Citric_acid_cycle).

However, whereas acetyl-CoA enters the citric acid cycle by condensing with an existing molecule of oxaloacetate, succinyl-CoA enters the cycle as a principal in its own right. Thus the succinate just adds to the population of circulating molecules in the cycle and undergoes no net metabolization while in it. When this infusion of citric acid cycle intermediates exceeds [cataplerotic](https://en.wikipedia.org/wiki/Cataplerosis) demand (such as for [aspartate](https://en.wikipedia.org/wiki/Aspartate) or [glutamate](https://en.wikipedia.org/wiki/Glutamate) synthesis), some of them can be extracted to the [gluconeogenesis](https://en.wikipedia.org/wiki/Gluconeogenesis) pathway, in the liver and kidneys, through [phosphoenolpyruvate carboxykinase](https://en.wikipedia.org/wiki/Phosphoenolpyruvate_carboxykinase), and converted to free glucose.[[10]](https://en.wikipedia.org/wiki/Beta_oxidation#cite_note-10)

**Unsaturated fatty acids**

β-Oxidation of unsaturated fatty acids poses a problem since the location of a cis bond can prevent the formation of a trans-Δ2 bond. These situations are handled by an additional two enzymes, [Enoyl CoA isomerase](https://en.wikipedia.org/wiki/Enoyl_CoA_isomerase) or [2,4 Dienoyl CoA reductase](https://en.wikipedia.org/wiki/2%2C4_Dienoyl_CoA_reductase).



Complete beta oxidation of [linoleic acid](https://en.wikipedia.org/wiki/Linoleic_acid) (an unsaturated fatty acid).

Whatever the conformation of the hydrocarbon chain, β-oxidation occurs normally until the acyl CoA (because of the presence of a double bond) is not an appropriate substrate for [acyl CoA dehydrogenase](https://en.wikipedia.org/wiki/Acyl_CoA_dehydrogenase), or [enoyl CoA hydratase](https://en.wikipedia.org/wiki/Enoyl_CoA_hydratase):

* If the acyl CoA contains a *cis-Δ3 bond*, then *cis-Δ3*-[Enoyl CoA isomerase](https://en.wikipedia.org/wiki/Enoyl_CoA_isomerase) will convert the bond to a *trans-Δ2* bond, which is a regular substrate.
* If the acyl CoA contains a *cis-Δ4 double bond*, then its dehydrogenation yields a 2,4-dienoyl intermediate, which is not a substrate for enoyl CoA hydratase. However, the enzyme [2,4 Dienoyl CoA reductase](https://en.wikipedia.org/wiki/2%2C4_Dienoyl_CoA_reductase) reduces the intermediate, using NADPH, into *trans-Δ3*-enoyl CoA. As in the above case, this compound is converted into a suitable intermediate by 3,2-Enoyl CoA isomerase.
* Odd-numbered double bonds are handled by the isomerase.
* Even-numbered double bonds by the reductase (which creates an odd-numbered double bond)

**Peroxisomal beta-oxidation**

Fatty acid oxidation also occurs in [peroxisomes](https://en.wikipedia.org/wiki/Peroxisome) when the fatty acid chains are too long to be handled by the mitochondria. The same enzymes are used in peroxisomes as in the mitochondrial matrix, and acetyl-CoA is generated. It is believed that very long chain (greater than C-22) fatty acids, branched fatty acids, some [prostaglandins](https://en.wikipedia.org/wiki/Prostaglandin) and [leukotrienes](https://en.wikipedia.org/wiki/Leukotriene) undergo initial oxidation in peroxisomes until [octanoyl-CoA](https://en.wikipedia.org/wiki/Octanoyl-CoA) is formed, at which point it undergoes mitochondrial oxidation.

One significant difference is that oxidation in peroxisomes is not coupled to [ATP](https://en.wikipedia.org/wiki/Adenosine_triphosphate) synthesis. Instead, the high-potential electrons are transferred to O2, which yields H2O2. It does generate heat however. The enzyme [catalase](https://en.wikipedia.org/wiki/Catalase), found primarily in peroxisomes and the [cytosol](https://en.wikipedia.org/wiki/Cytosol) of [erythrocytes](https://en.wikipedia.org/wiki/Erythrocyte) (and sometimes in [mitochondria](https://en.wikipedia.org/wiki/Mitochondria)), converts the [hydrogen peroxide](https://en.wikipedia.org/wiki/Hydrogen_peroxide) into [water](https://en.wikipedia.org/wiki/Water) and [oxygen](https://en.wikipedia.org/wiki/Oxygen).

Peroxisomal β-oxidation also requires enzymes specific to the peroxisome and to very long fatty acids. There are four key differences between the enzymes used for mitochondrial and peroxisomal β-oxidation:

1. The NADH formed in the third oxidative step cannot be reoxidized in the peroxisome, so reducing equivalents are exported to the cytosol.
2. β-oxidation in the peroxisome requires the use of a peroxisomal [carnitine acyltransferase](https://en.wikipedia.org/wiki/Carnitine_acyltransferase) (instead of carnitine acyltransferase I and II used by the mitochondria) for transport of the activated acyl group into the mitochondria for further breakdown.
3. The first oxidation step in the peroxisome is catalyzed by the enzyme [acyl-CoA oxidase](https://en.wikipedia.org/wiki/Acyl-CoA_oxidase).
4. The [β-ketothiolase](https://en.wikipedia.org/wiki/%CE%92-ketothiolase) used in peroxisomal β-oxidation has an altered substrate specificity, different from the mitochondrial [β-ketothiolase](https://en.wikipedia.org/wiki/%CE%92-ketothiolase).

Peroxisomal oxidation is induced by a high-fat diet and administration of hypolipidemic drugs like [clofibrate](https://en.wikipedia.org/wiki/Clofibrate).

**Energy yield**

The ATP yield for every oxidation cycle is theoretically a maximum yield of 17, as NADH produces 3 ATP, FADH2 produces 2 ATP and a full rotation of the citric acid cycle produces 12 ATP.In practice it is closer to 14 ATP for a full oxidation cycle as the theoretical yield is not attained - it is generally closer to 2.5 ATP per NADH molecule produced, 1.5 ATP for each FADH2 molecule produced and this equates to 10 ATP per cycle of the TCA(according to the [P/O ratio](https://en.wikipedia.org/wiki/P/O_ratio)), broken down as follows:

|  |  |  |
| --- | --- | --- |
| **Source** | **ATP** | **Total**  |
| 1 [FADH2](https://en.wikipedia.org/wiki/FADH2) | x 1.5 ATP | = 1.5 ATP (Theoretically 2 ATP)  |
| 1 [NADH](https://en.wikipedia.org/wiki/NADH) | x 2.5 ATP | = 2.5 ATP (Theoretically 3 ATP)  |
| 1 [acetyl CoA](https://en.wikipedia.org/wiki/Acetyl_CoA) | x 10 ATP | = 10 ATP (Theoretically 12 ATP |
| TOTAL |  | = 14 ATP  |

For an even-numbered saturated fat (C2n), n - 1 oxidations are necessary, and the final process yields an additional acetyl CoA. In addition, two equivalents of [ATP](https://en.wikipedia.org/wiki/Adenosine_triphosphate) are lost during the activation of the fatty acid. Therefore, the total ATP yield can be stated as:

(n - 1) \* 14 + 10 - 2 = total ATP

or

14n-6 (alternatively)

For instance, the ATP yield of [palmitate](https://en.wikipedia.org/wiki/Palmitate) (C16, *n = 8*) is:

(8 - 1) \* 14 + 10 - 2 = 106 ATP

Represented in table form:

|  |  |  |
| --- | --- | --- |
| **Source** | **ATP** | **Total**  |
| 7 FADH2 | x 1.5 ATP | = 10.5 ATP  |
| 7 NADH | x 2.5 ATP | = 17.5 ATP  |
| 8 acetyl CoA | x 10 ATP | = 80 ATP  |
| Activation |  | = -2 ATP  |
| NET |  | = 106 ATP  |

For sources that use the larger ATP production numbers described above, the total would be 129 ATP ={(8-1)\*17+12-2} equivalents per palmitate.

Beta-oxidation of unsaturated fatty acids changes the ATP yield due to the requirement of two possible additional enzymes.

**Similarities between beta-oxidation and citric acid cycle**

The reactions of beta oxidation and part of citric acid cycle present structural similarities in three of four reactions of the beta oxidation: the oxidation by FAD, the hydration, and the oxidation by NAD+. Each enzyme of these metabolic pathways presents structural similarity.

Step1;



A diagrammatic illustration of the process of lipolysis (in a fat cell) induced by high [epinephrine](https://en.wikipedia.org/wiki/Epinephrine) and low [insulin](https://en.wikipedia.org/wiki/Insulin) levels in the blood. Epinephrine binds to a [beta-adrenergic](https://en.wikipedia.org/wiki/Adrenergic_receptor#β_receptors) receptor in the cell wall of the adipocyte, which causes [cAMP](https://en.wikipedia.org/wiki/Cyclic_adenosine_monophosphate) to be generated inside the cell. The cAMP activates a [protein kinase](https://en.wikipedia.org/wiki/Protein_kinase), which phosphorylates and thus, in turn, activates a [hormone-sensitive lipase](https://en.wikipedia.org/wiki/Hormone-sensitive_lipase) in the fat cell. This lipase cleaves free fatty acids from their attachment to glycerol in the fat stored in the fat droplet of the adipocyte. The free fatty acids and glycerol are then released into the blood.

Step 2;



A diagrammatic illustration of the transport of [free fatty acids](https://en.wikipedia.org/wiki/Free_fatty_acids) in the blood attached to [plasma albumin](https://en.wikipedia.org/wiki/Serum_albumin), its diffusion across the cell membrane using a protein transporter, and its activation, using [ATP](https://en.wikipedia.org/wiki/Adenosine_triphosphate), to form [acyl-CoA](https://en.wikipedia.org/wiki/Acyl-CoA) in the [cytosol](https://en.wikipedia.org/wiki/Cytosol). The illustration is, for diagrammatic purposes, of a 12 carbon fatty acid. Most fatty acids in human plasma are 16 or 18 carbon atoms lon.

Step 3.



A diagrammatic illustration of the transfer of an acyl-CoA molecule across the inner membrane of the [mitochondrion](https://en.wikipedia.org/wiki/Mitochondrion) by [carnitine-acyl-CoA transferase](https://en.wikipedia.org/wiki/Carnitine_O-palmitoyltransferase) (CAT). The illustrated acyl chain is, for diagrammatic purposes, only 12 carbon atoms long. Most fatty acids in human plasma are 16 or 18 carbon atoms long. CAT is inhibited by high concentrations of [malonyl-CoA](https://en.wikipedia.org/wiki/Malonyl-CoA) (the first committed step in [fatty acid synthesis](https://en.wikipedia.org/wiki/Fatty_acid_synthesis)) in the cytoplasm. This means that fatty acid synthesis and fatty acid catabolism cannot occur simultaneously in any given cell.

Step 4;



A diagrammatic illustration of the process of the [beta-oxidation](https://en.wikipedia.org/wiki/Beta-oxidation) of an acyl-CoA molecule in the mitochodrial matrix. During this process an acyl-CoA molecule which is 2 carbons shorter than it was at the beginning of the process is formed. Acetyl-CoA, water and 5 [ATP](https://en.wikipedia.org/wiki/Adenosine_triphosphate) molecules are the other products of each beta-oxidative event, until the entire acyl-CoA molecule has been reduced to a set of [acetyl-CoA](https://en.wikipedia.org/wiki/Acetyl-CoA) molecules.

**Clinical significance**

There are at least 25 enzymes and specific transport proteins in the β-oxidation pathway.[[15]](https://en.wikipedia.org/wiki/Beta_oxidation#cite_note-Tein2013-15) Of these, 18 have been associated with human disease as [inborn errors of metabolism](https://en.wikipedia.org/wiki/Inborn_error_of_metabolism).