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# Lipid Metabolism



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# Oxidation of Fatty Acids

- Fatty acids undergo oxidative degradation known as  $\alpha$ ,  $\beta$ , and omega pathways
- $\alpha$  oxidation is found in brain tissue of animals and plants and results in removal of one carbon at a time from carboxyl end of the fatty acid
- Involved in the degradation of long chain fatty acids and is the main source of odd carbon fatty acids (C13 to C18)



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# Oxidation of fatty acids

- Omega oxidation is a minor pathway brought about by hydroxylase enzymes involving cytochrome P-450 in the endoplasmic reticulum
- Fatty acids occur as constituents of cutin and suberin
- $\beta$  oxidation takes place in mitochondria and fatty acids are activated before entering into oxidation
- **Activation of fatty acids**
  - FA's are converted into active intermediate in a reaction involving ATP and coenzyme A



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# $\beta$ oxidation of Fatty Acids

- Thioester linkage between carboxyl group of fatty acid and sulfhydryl group of coenzyme A is formed with hydrolysis of ATP
- Reaction takes place on the outer mitochondrial membrane catalysed by acyl CoA synthetase
- **Penetration of fatty acids into mitochondria**
  - Long chain acyl – CoA molecules are carried across the mitochondrial membrane by conjugating with carnitine - (a zwitterionic compound formed from lysine) acylcarnitines
  - Lower fatty acids oxidation occur within mitochondria without carnitine



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# $\beta$ oxidation of Fatty Acids

- Acyl CoA combines with carnitine in the presence of carnitine acyltransferase I
- Acylcarnitine is transported coupled with transport out of one molecule of carnitine
- Acylcarnitine reacts with coenzyme A catalysed by carnitine palmitoyl transferase II located inside of the inner membrane
- Acyl CoA is reformed in mitochondrial matrix with liberation of carnitine



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# $\beta$ oxidation of Fatty Acids

- **Oxidation** – 2 carbons are cleaved at a time from acyl CoA starting from carboxyl end
  - Chain is broken between  $\alpha$  and  $\beta$  carbon atoms
  - 2 carbon units of Acetyl coA is formed
  - Formation of  $\alpha, \beta$ -unsaturated acyl CoA in presence of acyl CoA dehydrogenase and the coenzyme FAD
  - Hydration of double bond between C-2 and C-3 by enoyl CoA hydratase forming  $\beta$ -hydroxy acyl CoA
  - $\beta$ -hydroxy acyl CoA is dehydrogenated in the presence of  $\beta$ -hydroxy acyl CoA dehydrogenase and  $\text{NAD}^+$  forming  $\beta$ -ketoacyl CoA



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# $\beta$ oxidation of Fatty Acids

- $\beta$ -ketoacyl CoA reacts with coenzyme A in presence of enzyme thiolase
- Products are acetyl CoA and acyl CoA containing 2 carbons less than original acyl CoA molecule
- Acetyl CoA formed is oxidised to carbondioxide and water by citric acid cycle
- **Oxidation of MUFA's**
  - Follows same reactions as that of SFA's with additional two enzymes isomerase and reductase



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# Oxidation of MUFA'S

- Oxidation of C-16 unsaturated palmitoleic acid having a single bond between c-9 and 10
- PA is activated and transported across mitochondrial membrane
- Undergoes 3 cycles of degradation, the cis decenoyl CoA formed does not serve as substrate
- Isomerase converts cis double bond into trans shifting the position of double bond between C-2&3
- The trans decenoyl CoA serves as substrate





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# Oxidation of PUFA's

- The cis c-3 bond formed after three rounds of  $\beta$  oxidation is converted into trans double bond by isomerase followed by  $\beta$  oxidation
- The acyl CoA produced contains C-4 double bond that undergoes dehydrogenation by acyl CoA dehydrogenase yielding trans C-2 and cis C-4 dienoyl intermediate
- Intermediate is converted to trans C-3 enoyl CoA and further to trans C-2 form that undergoes complete oxidation



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# Biosynthesis of Fatty Acids

- Synthesis occurs in cytosol, and intermediates are covalently linked to sulfhydryl group of acyl carrier protein (ACP)
- Enzymes involved in synthesis in animals are joined in a single polypeptide chain called fatty acid synthase and the reductant is NADPH
- **Steps in biosynthesis**
  - Acetyl CoA is catalyzed by acetyl CoA carboxylase having biotin as prosthetic group to malonyl CoA
  - **Formation of malonyl CoA is the initial and controlling step in FA synthesis** (bicarbonate serves as source of  $\text{CO}_2$ )



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# Steps in Biosynthesis of Fatty Acids

- Formation of Malonyl CoA occurs in two steps, carboxylation of biotin involving ATP and transfer of carboxyl group to acetyl CoA
  - Bicarbonate + acetyl CoA.....>malonyl CoA
- **Acetyl CoA carboxylase** plays a key role in regulating fatty acid metabolism
- Acetyl transacylase (can transfer acetyl and acyl groups) and malonyl transacylase (very specific) enzymes catalyse the formation of acetyl ACP and malonyl ACP



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# Steps in Biosynthesis of Fatty Acids

- Acetyl CoA + ACP.....>acetyl-ACP + COASH
- Malonyl CoA + ACP.....>malonyl-ACP + COASH
- Acetyl ACP condenses with malonyl ACP to form acetoacetyl ACP with elimination of CO<sub>2</sub>
- The β-keto group in acetoacetyl group is reduced by NADPH dependent β-ketoacyl reductase to β-hydroxyl acyl ACP
- β-hydroxyl group combines with hydrogen atom attached to γ carbon and a water molecule is removed to form α, β-unsaturated acyl ACP

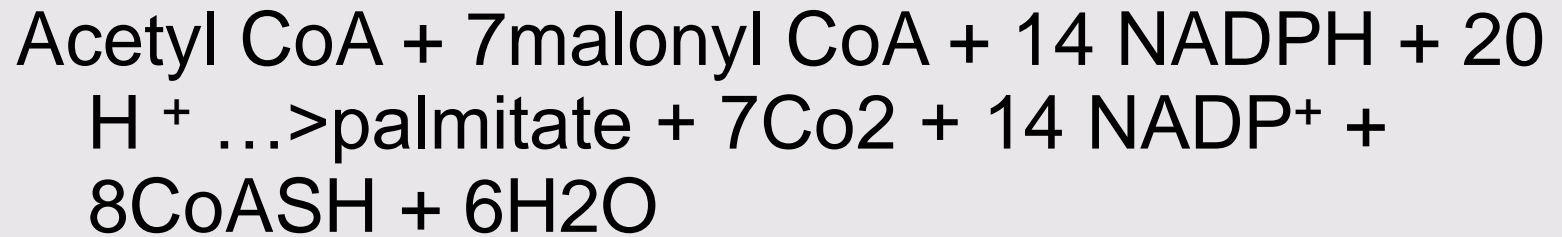


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# Steps in Biosynthesis of Fatty Acids

- Unsaturated Acyl ACP is converted to saturated acyl ACP by  $\alpha$ ,  $\beta$ -unsaturated acyl ACP reductase using NADPH as coenzyme
- The end product contains 2 atoms more and addition of subsequent acetyl units through malonyl ACP leads to formation of palmitate





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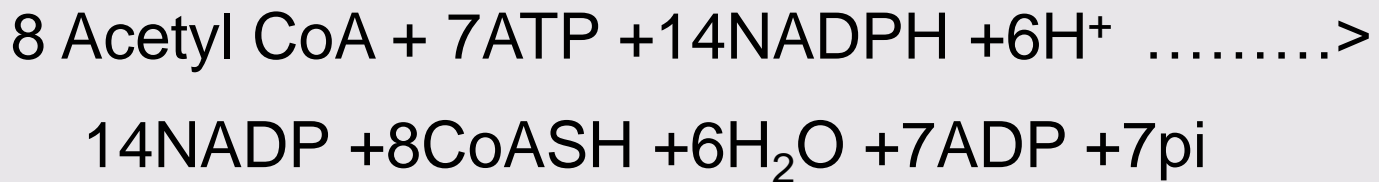
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# Steps in Biosynthesis of Fatty Acids

- Synthesis of malonyl CoA



Overall equation for synthesis of palmitate



Synthesis and degradation are not simultaneously active



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# Elongation or synthesis of long chain fatty acids

- Major product of fatty acid biosynthesis is 16 carbon palmitate
- Chain elongation reactions occur in mitochondria and microsomes (small membrane enclosed vesicles derived from ER)
- Microsomal system is significant as it provides long chain fatty acids (18-24C) required for myelination of nerve cells in animal system
- Elongation system adds 2 carbons to palmitoyl CoA to make steroyl CoA



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# Synthesis of Unsaturated FA's

- Palmitate and stearate serve as precursors for palmitoleate (16:1), and oleate (18:1) respectively
- Double bond is introduced into fatty acid chain by an oxidative reaction catalysed by fatty acyl-CoA desaturase which is NADPH dependent enzyme
- Desaturase oxidises phosphatidylcholine bound oleate to produce PUFA's
- Linoleic and linolenic are not synthesized by mammals but synthesized by plants
- After ingestion linoleate are converted to  $\gamma$ linoleate, arachidonic acid in animals





# Synthesis of Triacylglycerol

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## • **Activation of glycerol**

- Glycerol kinase catalyses the activation of glycerol to glycerol-3-phosphate
- If GK is in low quantity, G3P is formed from DHAP
- Dihydroxyacetone phosphate is converted to glycerol-3-phosphate catalyzed by glycerol-3-phosphate dehydrogenase with formation of NAD<sup>+</sup>

## • **Activation of Fatty Acids**

- FA's are activated to acyl CoA by acylCoA synthetase utilizing ATP and CoASH



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# Activation of FA's

- Two molecules of Acyl CoA combine with glycerol-3-phosphate to form 1,2-diacylglycerol phosphate
- Phosphate group is removed by phosphatidate phosphatase to form 1,2-diacyl glycerol
- Esterification of one or more molecule of acyl CoA with diacylglycerol results in formation of triacylglycerol
- The alternate pathway involves reduction of DHAP by NADPH, acylated and converted to lysophosphatidate (accounts for less than 10%)



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# Peroxidation

- Lipid peroxidation is described as a process under which oxidants such as free radicals attack lipids containing double bonds (PUFA's)
- Overall process consists of three steps: initiation, propagation, and termination
- **Initiation** – peroxidants like hydroxyl radical abstracts hydrogen forming lipid radical ( $L^*$ )
- **Propagation** – lipid radical reacts with oxygen to form lipid peroxy radical ( $LOO^*$ ) removing hydrogen from another lipid molecule generating  $L^*$  and lipid hydroperoxide ( $LOOH$ )



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# Lipid Peroxidation

- **Termination** – antioxidants like vitamin E donate a hydrogen atom to  $\text{LOO}^*$  forming a corresponding vitamin E radical
- Vitamin E radical reacts with another  $\text{LOO}^*$  forming nonradical products
- Primary products of peroxidation are  $\text{LOOH}$
- Secondary products formed include malondialdehyde (MDA), propanal, hexanal, and 4-hydroxynonenal (4-HNE)

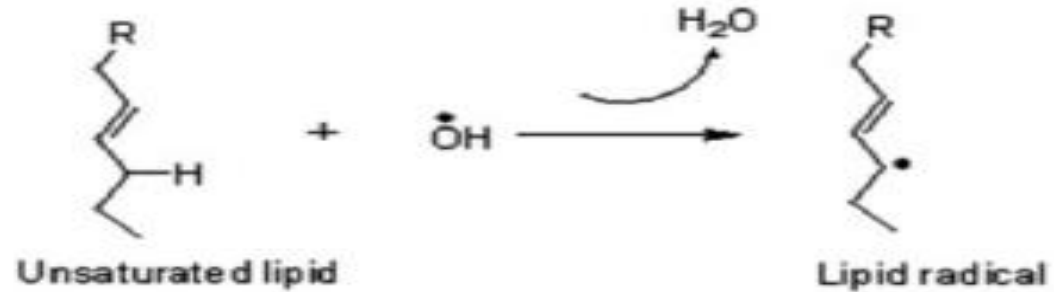


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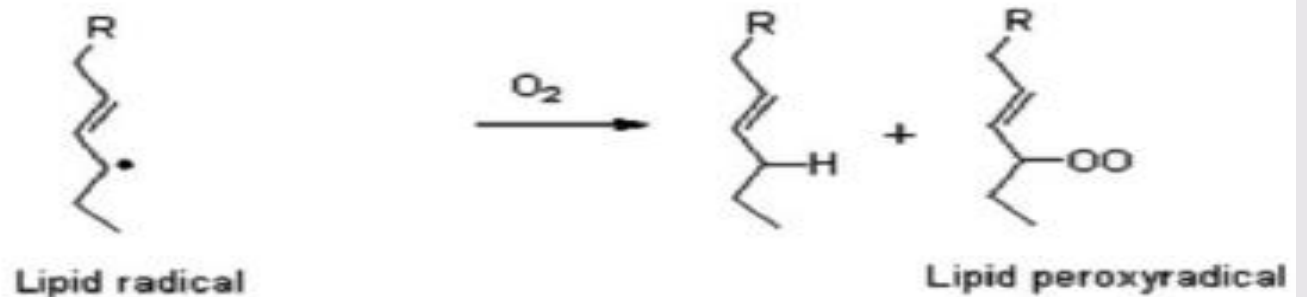
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# Lipid Peroxidation

## Initiation



## Propagation



## Termination

