LIPIDS

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TO MY STUDENTS

HERE I HAVE TRIED TO SIMPLIFY THE HUGE SUBJECT WITH ANIMATIONS, DIAGRAMS, FLOW CHARTS & RELEVENT MCQs.

DIFFERENT TEXT BOOKS AND REFERENCE BOOKS HAVE BEEN USED FOR PREPARING THE CONTENTS.

REMEMBERTHESE SLIDES ARE NOT THE SUBSTITUTE OF YOUR TEXT BOOKS

ANIMATIONS AND DIAGRAMS ARE COLLECTED FROM DIFFERENT WEBSITE SOLELY FOR EDUCATION PURPOSE.

Lipids are non-polar (hydrophobic) compounds, soluble in organic solvents.

Classification of Lipids

1. Simple Lipids

A. Neutral fats - Triglycerides
B. Waxes

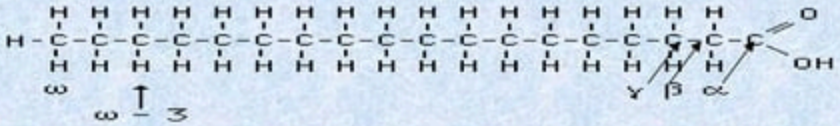
2. Conjugated Lipids (polar lipids)

A. **Phospholipids** - contain a phosphoric acid molecule and a fat molecule.
B. Glycolipid- contain a carbohydrate and a fat molecule.
   cerebrosides
   globosides
   gangliosides
C. Sulfolipids - contain a sulfate radical.
D. lipoprotein

3. Derived Lipids

A. Fatty acids
B. Glycerol
C. Cholesterol and other steroid (Vit. D)
D. Vitamins A, E, K

Fatty acids consist of a hydrocarbon chain with a carboxylic acid at one end.
Chain length from C4 to C24.



Use of Greek letters to designate carbons

The carbon next to the −COOH group is designated α; the next one is β, and so forth. The most distant carbon is designated ω. Sometimes carbon atoms close to the ω carbon are designated in relation to it. *E.g.*, the third from the end is ω − 3 (omega minus 3).

Alternatively,C atoms are numbered from COOH C is no. 1 ,

The Length of the Carbon Chain

long-chain(16-above), medium-chain(8-14), short-chain(2-6)

The Degree of Unsaturation

~saturated

~unsaturated -- monounsaturated, polyunsaturated

The Location of Double Bonds

omega-3 fatty acid, omega-6 fatty acid

Branched ,hydroxy, cyclic

Saturated fatty acids

Name end in **"Anoic".**

Acetic	2
Propinoic	3(OCFA)iso-BCFA
Butyric	4
Valeric	5(OCFA)iso-BCFA
Caproic	6
Caprilic	8
Capric	10
Lauric	12
Myristic	14
Palmitic	16(25%)
Stearic	18(5%)
Arachidic	20
Lignoceric	24

Unsaturated fatty acids

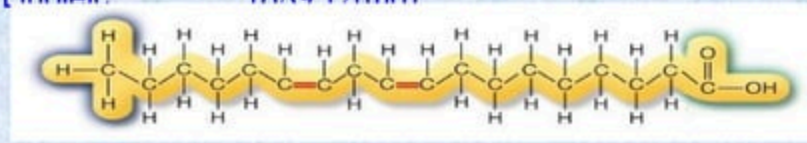
Name end in **"Enoic"**

Monounsaturated

Palmitoleic	16 Δ9(ω7)
Oleic	18Δ9(ω9)
Erucic	22Δ13(ω9)
Nervonic	24Δ15(ω9)

Polyunsaturated

Linoleic 18Δ9,12(ω6)



α- linolenic	18 Δ9,12,15(ω3) (γ-Δ9,12,6(ω6))
Arachidonic	20 Δ5,10,11,14(ω6)
Timnodonic	20 Δ5,8,11,14,17(ω3)EPA
Clupanodonic	22 Δ7,10,13,16,19(ω3)DPA
Cervonic	22 Δ4,7,10,13,16,19(ω3)DHA

Omega-3:

Eicosopentaenoic acid (EPA)

Docosahexaenoic acid (DHA)

Alpha-linolenic acid (ALA)

flaxseed--most, canola (rapeseed), soybean, walnut, wheat germ

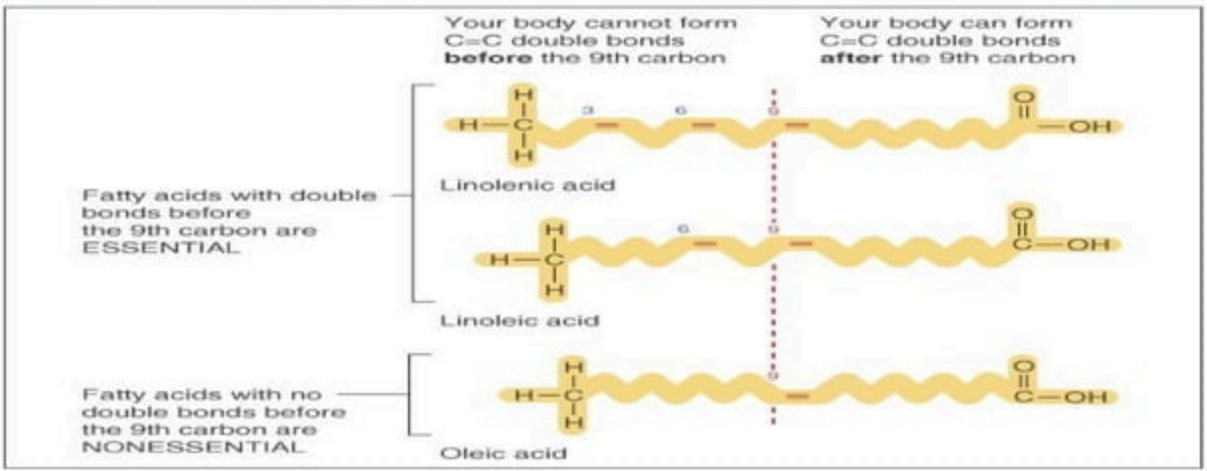
body can make some EPA and DHA from ALA

Omega-6

corn, safflower, cottonseed, sesame, sunflower

Linoleic acid

Introduction of first double bond is always at or near $\Delta 9$ by desaturase in presence of O2,NADH,cyt b5.



Omega-3 Fatty Acids

~Associated with:
anti-inflammatory, antithrombotic, antiarrhythmic, hypolipidemic, vasodilatory properties

~Inflammatory conditions
~Ulcerative colitis, Crohn's
~Cardiovascular disease
~Type 2 diabetes
~Renal disease

* Mental function
* Growth and development

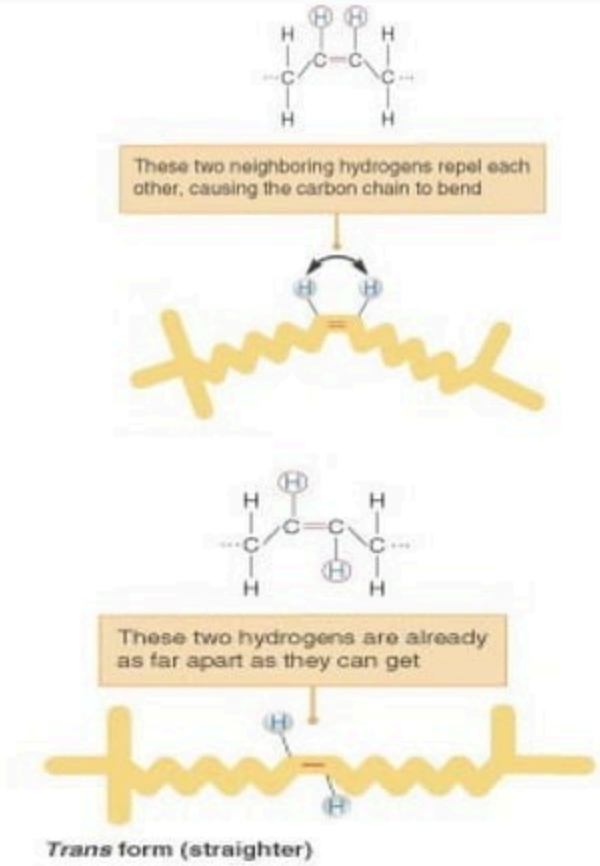
Essential Fatty Acid Deficiency

~Classical symptoms include:
growth retardation, reproductive failure, skin lesions, kidney and liver disorders, subtle neurological and visual problems

~People with chronic intestinal diseases

~Depression-inadequate intake alters brain activity or depression alters fatty acid metabolism

~Attention Deficit Hyperactivity Disorder
~lower levels of omega-3--more behavioral problems



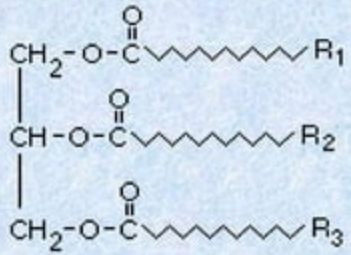
Geometric isomerism

Cis-configuration—naturally occuring

Trans-form—metabolic intermediate.

By product of saturation of FA 'hardening'

Triacylglycerol



A triacylglycerol

R_1 is often palmitate.
R_2 is often oleate.
R_3 is often oleate or a polyunsaturated fatty acyl group.

~Esters of trihydric alcohol,glycerol with various fatty acid.

~fatty acids are stored primarily in adipocytes as triacylglycerol.

~Triacylglycerol must be hydrolyzed to release the fatty acids.

~Adipocytes are found mostly in the abdominal cavity and subcutaneous tissue.

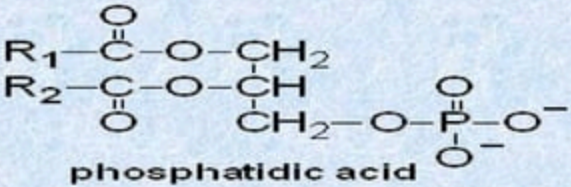
~Adipocytes are metabolically very active; their stored triacylglycerol is constantly hydrolyzed and resynthesized

~role of HORMONE SENSITIVE LIPASE

PHOSPHOLIPIDS

Phospholipids are synthesized by esterification of an alcohol to the phosphate of phosphatidic acid (1,2-diacylglycerol 3-phosphate).

Most phospholipids have a saturated fatty acid on C-1 and an unsaturated fatty acid on C-2 of the glycerol backbone



phosphatidic acid

Simplest phospholipid

CLASSIFICATION

LONG CHAIN ALCOHOL CONTAINING

plasmalogen

ALCOHOL SPHINGOSINE

sphingomyelin

NITROGEN CONTAINING GLYCERO PHOSPHATIDS

~lecithin

~Cephalin

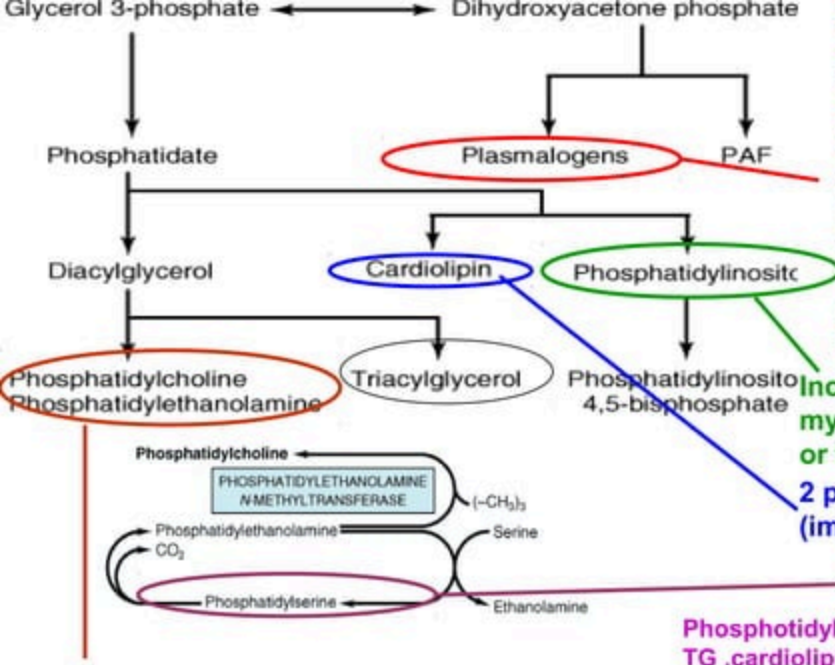
~Phosphotidyl serine

NON-NITROGEN CONTAINING GLYCERO PHOSPHATIDS

~PHOSPHATIDYL INOSITOL

~PHOSPHATIDYL GLYCEROL

~CARDIOLIPIN



Plasmalogens are glycerol ether phospholipids. 3 classes :choline, ethanolamine and serine plasmalogens. Ethanolamine (prevalent in myelin). Choline (cardiac tissue). choline plasmalogen (1-alkyl, 2-acetyl phosphatidylcholine) biological mediator, inducing cellular (concentrations as low as 10^{-11} M. platelet activating factor, PAF

Inositol as alcohol,isomeric form: myoinositol,biomembrane(precursor for IP3)

2 phosphatidic acid+ glycerol (imm;myocardium)

Serine as N base,CNS

Phosphotidyl glycerol: intermediate in syn. Of TG ,cardiolipin,(diphosphotidyl glycerol)

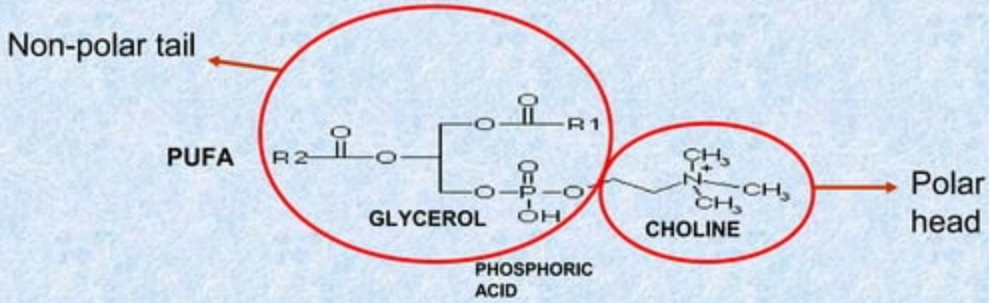
Ethanolamine as N base, association with lecithin:CNS,amphipha tic

Phospholipids synthesized --two mechanisms.

~CDP-activated polar head group for attachment to the phosphate of phosphatidic acid.

~The other utilizes CDP-activated 1,2-diacylglycerol and an inactivated polar head group.

PHOSPHOTIDYL CHOLINE OR LECITHIN



class of phospholipids :called the lecithins.

Most **abundant** in cell membrane

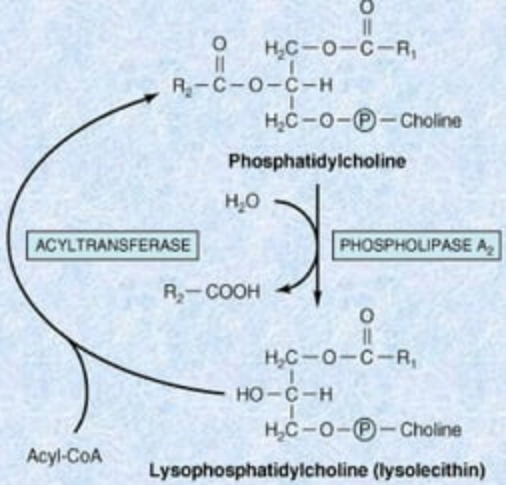
At physiological pH, **neutral zwitterions**.

palmitic or **stearic** acid at carbon 1

oleic, linoleic or linolenic acid at carbon 2.

dipalmitoyllecithin :pulmonary surfactant. It contains palmitate at both carbon 1 and 2 of glycerol.

Choline is activated first by phosphorylation and then by coupling to CDP prior to attachment to phosphatidic acid.



~Phospholipase A_2 catalyses hydrolysis of glycerophospholipid.

~**Lysophospholipid** may be reacetylated or attacked by lysophospholipase and ultimate degradation to glycerol-3-P plus base.

~Alternatevely, lysolecithin may be formed by **LCAT**(lysolecithin chosterol acyl transferase.(transfer of PUFA from 2nd C to cholesterol.

~Detergent and **hemolytic agent**.

~account for hemolysis and renal failure in viper poisoning

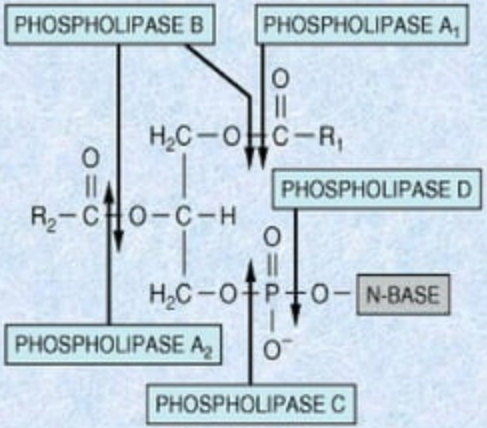
A_1 :human,cobra venom

A_2 :human pancreatic fluid,venom

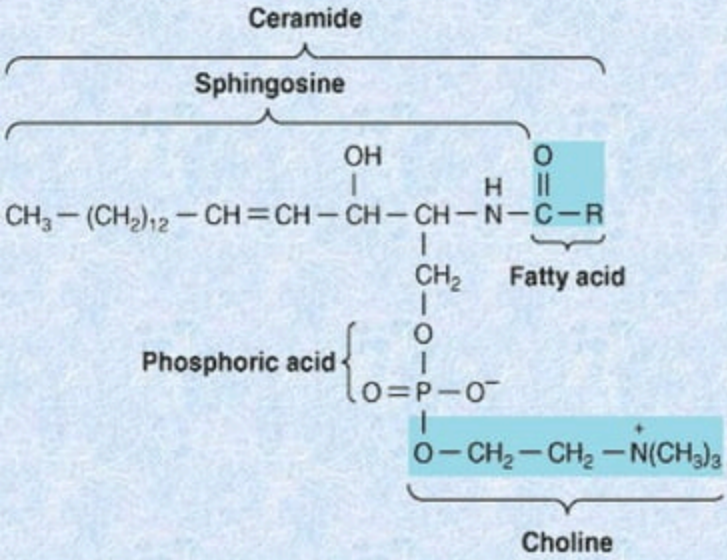
B :association with A, *aspergillus sp., penicillum notatum*

C :major constituent of bacterial toxin

D :plants,mammalian signal transduction.



PHOSPHOSPINGOLIPID/SPHINGOMYELIN



CERAMIDE IS SYNTHESISED IN ER FROM SERINE

IMP. SIGNALLING MOLECULE

REGULATES PATHWAYS(PCD,CELL CYCLE,CELL DIFFERENTIATION)

CERAMIDE+PHOSPHOTIDYL CHOLINE--- (GOLGI APPARATUS)

SPHINGOMYELINASE IS THE ENZ. REQ. FOR DEGRADATION , DEFICIENCY—NIEMANN PICK DISEASE

GLYCOLIPIDS

CARBOHYDRATE AND CERAMIDE(SPHINGOSINE+FATTY ACID)NO PHOSPHORIC ACID

1. CEREBROSIDE OR GLYCOSPHINGOSIDE OR CERAMIDE MONOHEXOSIDE

Nervous tissue,white matter,myelin sheath

Ceramide + glucose – glucocerebroside

Ceramide + galactose – galactocerebroside

Hydrolysis yield sugar , high MW FA, sphingosine

Types **KERASIN:** Lignoceric acid(n-Tetracosanoic acid ,C_{24} H_{45})

CEREBRON: hydroxy lignoceric (cerebronic acid)

NERVON:unsaturated nervonic acid

OXYNERVON; hydroxyderivative of nervonic acid

GAUCHERS DISEASE

2. GLOBOSIDES OR CERAMIDE OLIGOSACCHARIDE

Two or more hexose or hexoseamine attached to ceramide

Ceramide + glucose + galactose = lactosyl ceramide

Present in erythrocyte membrane

3.GANGLIOSIDES

Ceramide + glucose &/or gal + n-acetyl galactoseamine + NANA

CNS,spleen,RBC

MW 180000 to 250000 kd

Mono , di , trisialogangliosides present in brain

Types GM1,GM2,GM3 & GD3

GM3—simplest & common (ceramide+glu+gal+NANA)

GM1 intestine:receptor for cholera toxin

Receptor for circulating hormone

TAY SACH'S DISEASE

SULPHOLIPID

SULPHATED ESTERS OF GLYCOLIPID

SULPHATED CEREBROSIDE,SULPHATED GLOBOSIDE,SULPHATED GANGLIOSIDES

SULPHATE GRP. ESTERIFIED TO -OH OF HEXOSE

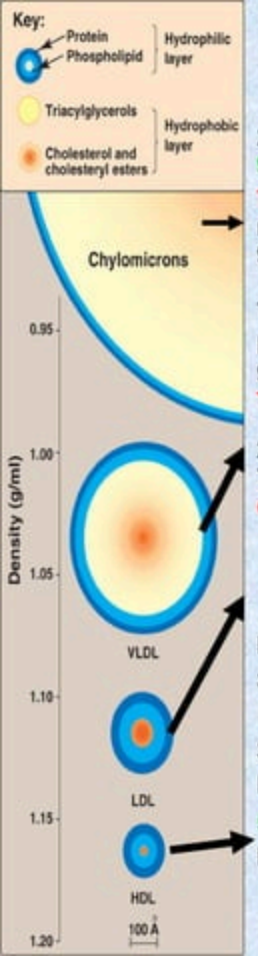
ABUNDANT IN WHITE MATTER OF BRAIN.

Disorders Associated with Abnormal Sphingolipid Metabolism

Disorder	Enzyme Deficiency	Accumulating Substance	Symptoms
Tay-Sachs disease	HexA	G_{M2} ganglioside	infantile form: rapidly progressing mental retardation, blindness, early mortality
Sandhoff disease	HexA and HexB	globoside; G_{M2} ganglioside	infantile form: same symptoms as Tay-Sachs, progresses more rapidly
Tay-Sachs AB variant			
G_{M2} activator deficiency	G_{M2} activator (GM2A)	G_{M2} ganglioside	infantile form: same symptoms as Tay-Sachs
Gaucher disease	acid β-glucosidase (glucocerebrosidase)	glucocerebrosides	hepatosplenomegaly, mental retardation in infantile form, long bone degeneration
Fabry disease	α-galactosidase A	globotriaosylceramide; also called ceramide trihexoside (CTH)	kidney failure, skin rashes
Niemann-Pick diseases			
Types A and B	sphingomyelinase	sphingomyelins	type A is severe disorder with heptosplenomegaly, severe neurological involvement leading to early death, type B only visceral involvement
Type C	NPC1 protein	LDL-derived cholesterol	

Disorder	Enzyme Deficiency	Accumulating Substance	Symptoms
Krabbe disease; globoid cell leukodystrophy (GLD)	galactocerebrosidase	galactocerebrosides	mental retardation, myelin deficiency
G_{M1}gangliosidosis	β-galactosidase-1	G_{M1} gangliosides	mental retardation, skeletal abnormalities, hepatomegaly
Metachromatic leukodystrophy; sulfatide lipodosis	arylsulfatase A	sulfatides	mental retardation, metachromasia of nerves
Fucosidosis	α-fucosidase	pentahexosylfucoglycolipid	cerebral degeneration, thickened skin, muscle spasticity
Farber lipogranulomata	acid ceramidase	ceramides	hepatosplenomegaly, painful swollen joints

LIPOPROTEIN



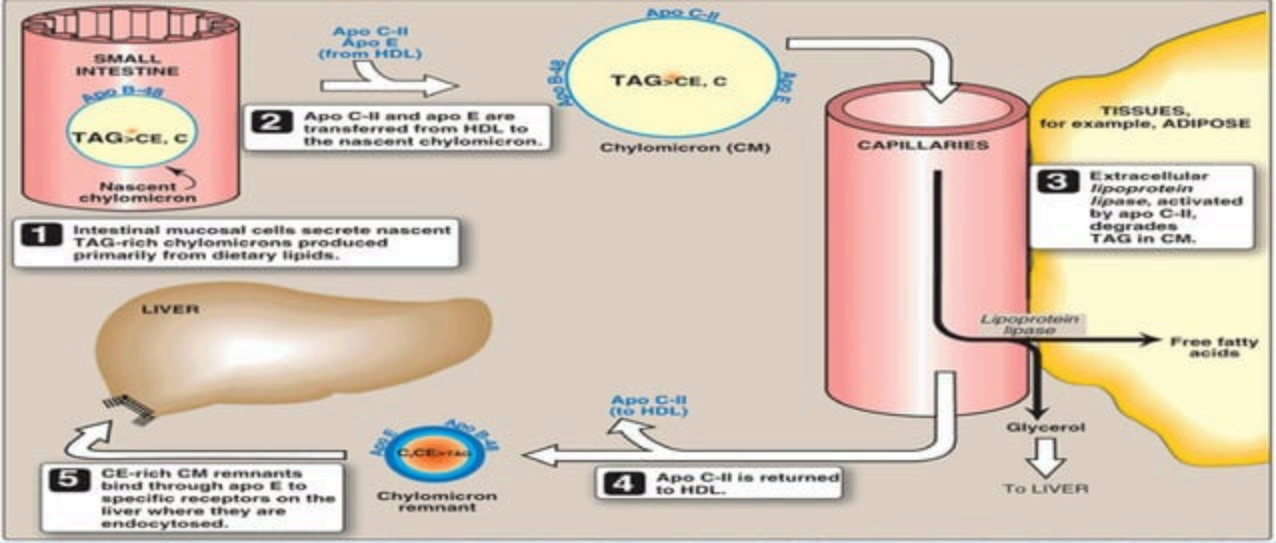
COMPOSITION	SOURCE	FROM	TO	APOPROTIENS	ELECTROPHORETIC MOBILITY
2%protein 98% lipid TAG exo remnants 92-94% lipid	intestine	GUT	PERIPHERAL TISSUE	AI,II,IV. B48 associated always, CI,II,III, E	ORIGIN
7-10% PROTEIN,90-93% LIPID TAG endo	Liver intestine	liver	PERIPHERAL TISSUE	B100 ,CI,II,III	PRE-β
21% protein 79% lipid cholesterol	Liver, intestine, VLDL, chylomicron	Liver	Heart	B100 RNA editing,same mRNA (B48 & B100)	BROAD-β
HDL HDL_1 32%-68% HDL_2 33%-67% HDL_3 57%-43% PRE- β HDL	LIVER INTESTINE VLDL CHYLOMICRON	HEART PL, CHOLESTEROL	LIVER	AI,II,IV CI,II,III, D, E AI	BETA

PLASMA LIPIDS

- Since lipids are insoluble in water, they need the help of carriers in Plasma.
- There fore they are complexed with protein to form Lipoproteins.
- The protein part is called apolipoprotein.
- Abbreviated as Lp.

Classification

- Chylomicrons
- VLDL (very low density lipoprotein)
- Intermediate density lipoproteins (IDL)
- Low density lipoproteins (LDL)
- High Density lipoproteins (HDL)
- Free fatty acids (complexed with albumin)



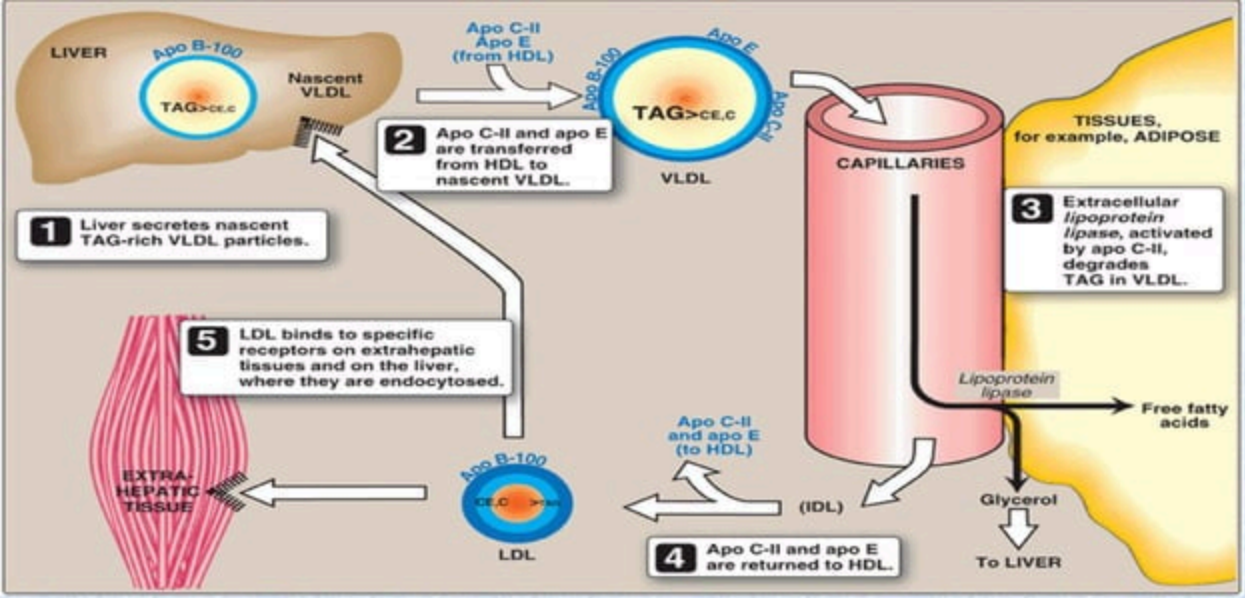
Chylomicrons assembled in **intestinal mucosal cells** from **dietary lipids**

nascent chylomicron particle has **apolipoprotein (apo) B-48**.

released from the intestinal cells into the lymphatic system --blood, receive **apo C-II** and **apo E** . Apo C-II activates **lipoprotein lipase**, which degrades the chylomicron's **triacylglycerol** to fatty acids and glycerol. The **fatty acids** are **stored** (in the **adipose**) or used for **energy** (by the **muscle**).

Patients with a **deficiency** of **lipoprotein lipase** or **apo C-II** show a dramatic accumulation of chylomic rons in the plasma

chylomicron remnant—carrying most of the **dietary cholesterol**—binds to a **receptor** on the **liver** that recognizes **apo E**. The particle is **endocytosed** and its contents degraded by **lysosomal**



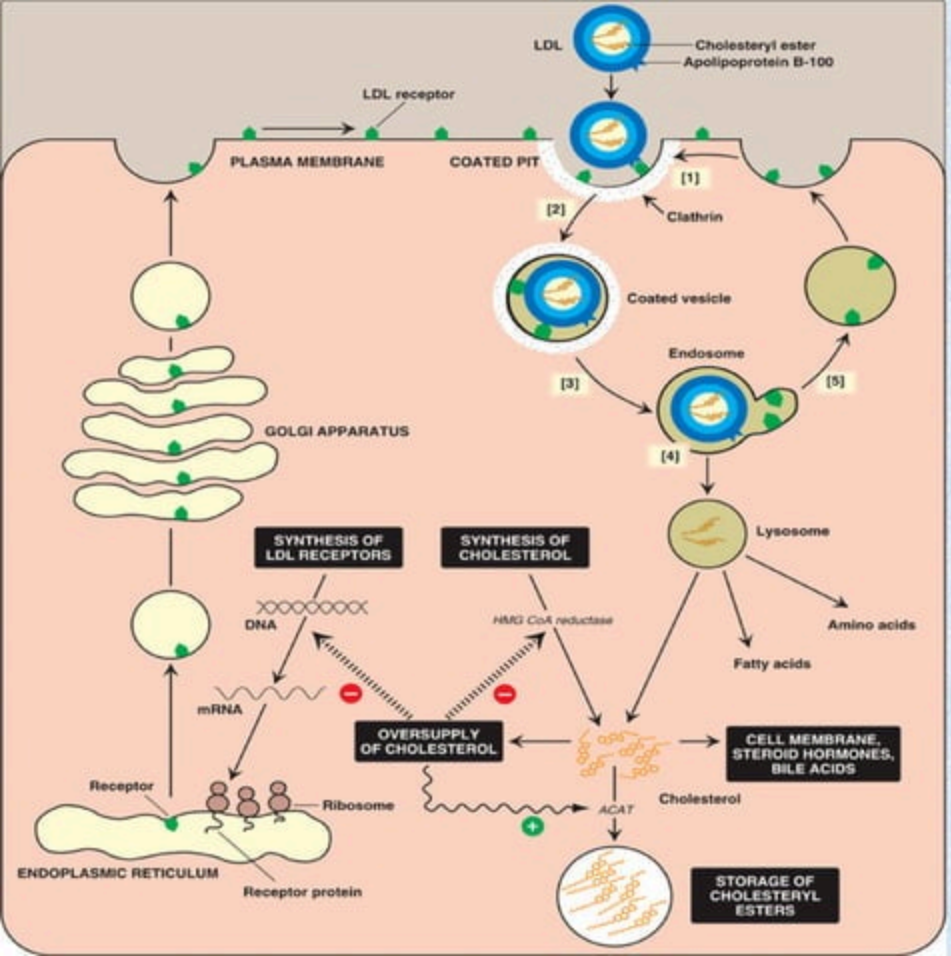
Nascent VLDL produced in liver, composed of triacylglycerol.

They contain a single molecule of apo B-100.

As triacylglycerol is removed from the VLDL, the particle receives (ApoE & C-II)from HDL. This process is accomplished by cholesteryl ester transfer protein.

Eventually, VLDL in the plasma is converted to **LDL**.

It carries triglycerides from liver to peripheral tissues for energy needs.



Apo C-II and apo E are returned to HDL

LDL retains **apo B-100**, which is recognized by **receptors** on **periph eral tissues** and the **liver**.(Half life period is two days)

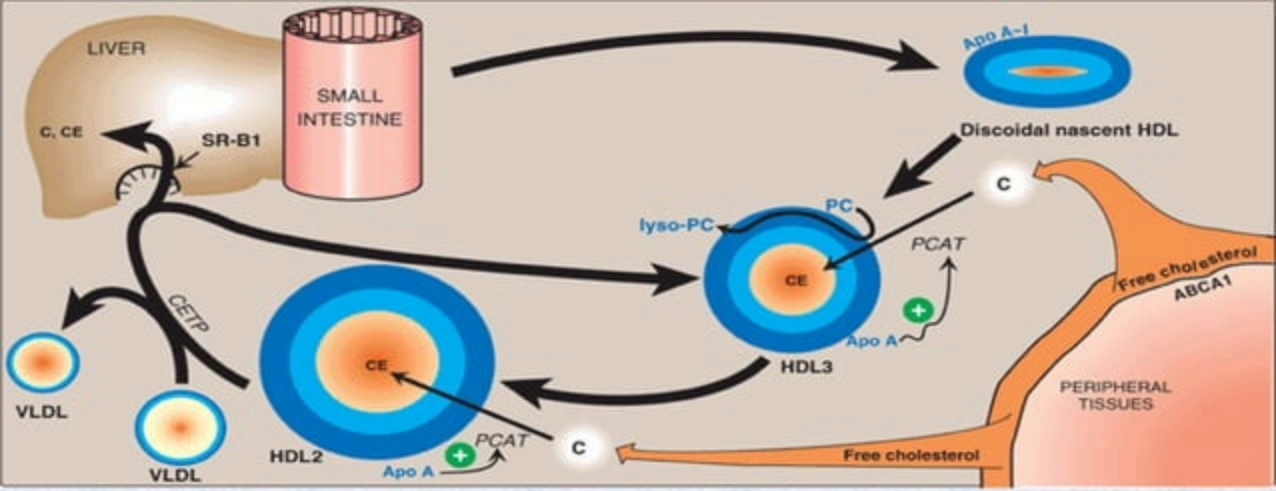
LDLundergo **receptor-mediated endocytosis**, and their contents are degraded in the **lysosomes**.

When lysosomal enzymes degrade apoproteins of LDL free cholesterols are liberated and receptors returned back to carry furhter LDL

LDL transports cholestrol from liver to the pheripheral tissues. .

Little Rascal

- Lp A?



HDL are created by **lipidation of apo A-1** synthesized in the **liver** and **intestine**. **Functions**

1) serving as a **circulating reservoir of apo C-II** and **apo E** for chylomicrons and VLDL;

2) removing **unesterified cholesterol** from cell surfaces and other lipoproteins and **esterifying it** using **phosphatidylcholine:cholesterol acyl transferase**, a liver-synthesized plasma enzyme that is activated by **apo A-1**

3) delivering these cholesteryl esters to the liver ("**reverse cholesterol transport**").

Hyperlipoproteinemias

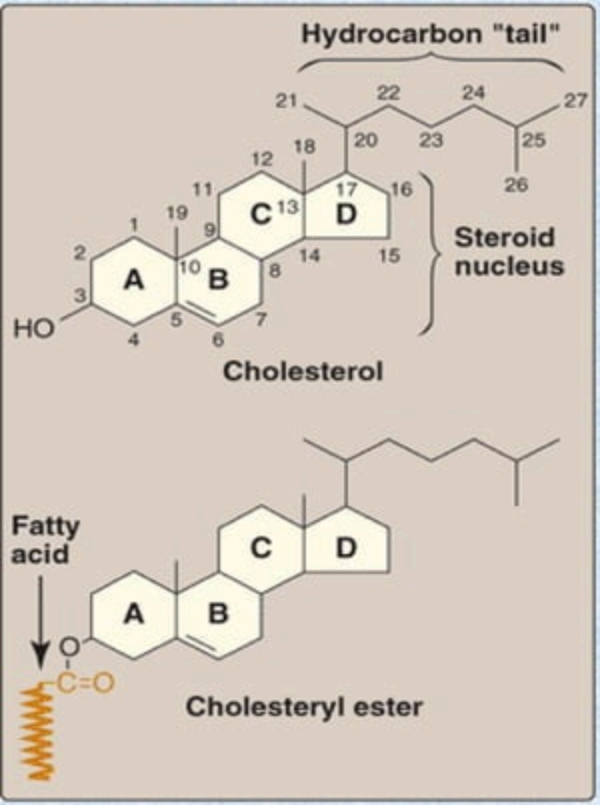
Disorder	Defect	Comments
Type I (familial LPL deficiency, familial hyperchylomicronemia)	(a) deficiency of LPL; (b) production of abnormal LPL; (c) apo-C-II deficiency	slow chylomicron clearance, reduced LDL and HDL levels; treated by low fat/complex carbohydrate diet; no increased risk of coronary artery disease
Type II (familial hypercholesterolemia, FH)	4 classes of LDL receptor defect	reduced LDL clearance leads to hypercholesterolemia, resulting in atherosclerosis and coronary artery disease
Type III (familial dysbetalipoproteinemia, remnant removal disease, broad beta disease, apolipoprotein E deficiency)	hepatic remnant clearance impaired due to apo-E abnormality; patients only express the apo-E_2 isoform that interacts poorly with the apo-E receptor	causes xanthomas, hypercholesterolemia and atherosclerosis in peripheral and coronary arteries due to elevated levels of chylomicrons and VLDLs
Type IV (familial hypertriacylglycerolemia)	elevated production of VLDL associated with glucose intolerance and hyperinsulinemia	frequently associated with type-II non-insulin dependent diabetes mellitus, obesity, alcoholism or administration of progestational hormones; elevated cholesterol as a result of increased VLDLs
Type V familial	elevated chylomicrons and VLDLs due to unknown cause	hypertriacylglycerolemia and hypercholesterolemia with decreased LDLs and HDLs

Disorder	Defect	Comments
Familial hyperalphalipoproteinemia	increased level of HDLs	a rare condition that is beneficial for health and longevity
Type II Familial hyperbetalipoproteinemia	increased LDL production and delayed clearance of triacylglycerols and fatty acids	strongly associated with increased risk of coronary artery disease
Familial ligand-defective apo-B	2 different mutations: Gln for Arg (amino acid 3500) or Cys for Arg (amino acid 3531); both lead to reduced affinity of LDL for LDL receptor	dramatic increase in LDL levels; no affect on HDL, VLDL or plasma triglyceride levels; significant cause of hypercholesterolemia and premature coronary artery disease
Familial LCAT deficiency	absence of LCAT leads to inability of HDLs to take up cholesterol (reverse cholesterol transport)	decreased levels of plasma cholesteryl esters and lysolecithin; abnormal LDLs (Lp-X) and VLDLs; symptoms also found associated with cholestasis
Wolman's disease (cholesteryl ester storage disease)	defect in lysosomal *cholesteryl ester hydrolase*; affects metabolism of LDLs	reduced LDL clearance leads to hypercholesterolemia, resulting in athersclerosis and coronary artery disease
Hormone-releasable hepatic lipase deficiency	deficiency of the lipase leads to accumulation of triacylglycerol-rich HDLs and VLDL remnants (IDLs)	causes xanthomas and coronary artery disease

Hypolipoproteinemias

Disorder	Defect	Comments
Abetalipoproteinemia(acanthocytosis, Bassen-Kornzweig syndrome)	no chylomicrons, VLDLs or LDLs due to defect in apo-B expression	rare defect; intestine and liver accumulate, malabsorption of fat, retinitis pigmentosa, ataxic neuropathic disease, erythrocytes have &quotthorny" appearance
Familial hypobetalipoproteinemia	at least 20 different apoB gene mutations identified, LDL concentrations 10-20% of normal, VLDL slightly lower, HDL normal	mild or no pathological changes
Familial alpha-lipoprotein deficiency (Tangier disease, Fish-eye disease, apo-A-I and -C-III deficiencies)	all of these related syndromes have reduced HDL concentrations, no effect on chylomicron or VLDL production	tendency to hypertriacylglycerolemia; some elevation in VLDLs; Fish-eye disease characterized by severe corneal opacity

CHOLESTEROL SYNTHESIS AND EXCRETION



Occurs as free (brain) and esterified (adrenal cortex)form.

Plasma membrane & lipoproteins.

Normal healthy adults synthesize --approximately 1g/day.

consume approximately 0.3g/day.

150 - 200 mg/dL is maintained in serum by controlling the level of *de novo* synthesis.

Cholesterol is utilized in the formation ~membranes .

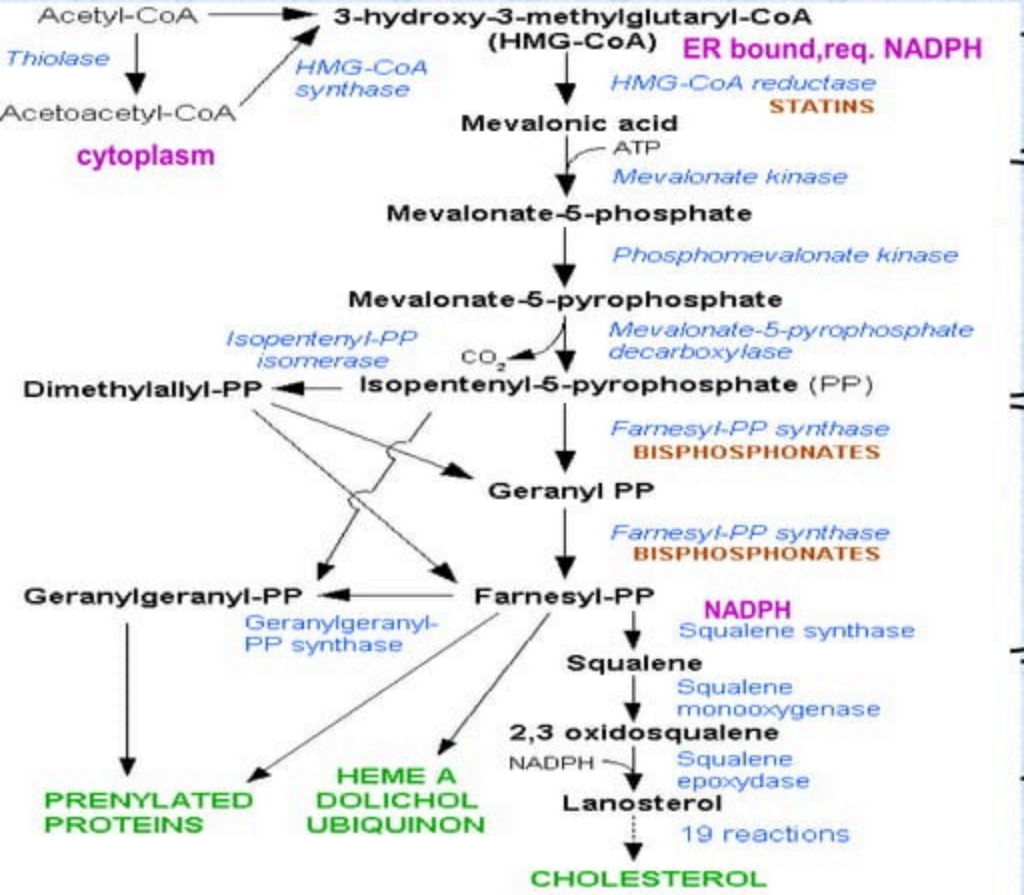
~synthesis of the steroid hormones .

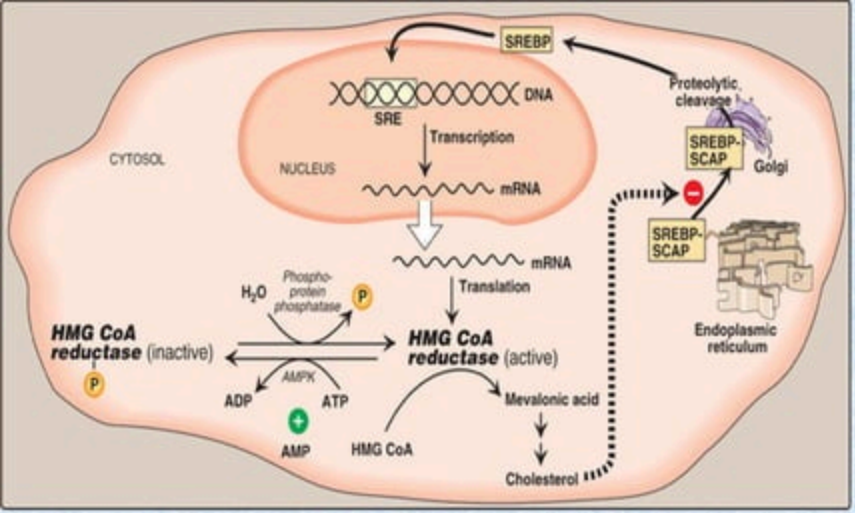
~bile acids (greatest proportion).

Colour reactions of sterols

- *Libermann-Burchard reaction*
- *Salkowski test*
- *Zak's reaction*

CHOLESTEROL BIOSYNTHESIS





The cellular supply of cholesterol maintained at

1. Regulation of ***HMG-CoA reductase***

2. excess intracellular free cholesterol through acylCoA:cholesterol acyltransferase, ACAT

3. plasma cholesterol levels LDL receptor-mediated uptake and HDL-mediated reverse transport.(esterification by LCAT)

STEROL DEPENDENT REGULATION OF GENE EXPRESSION

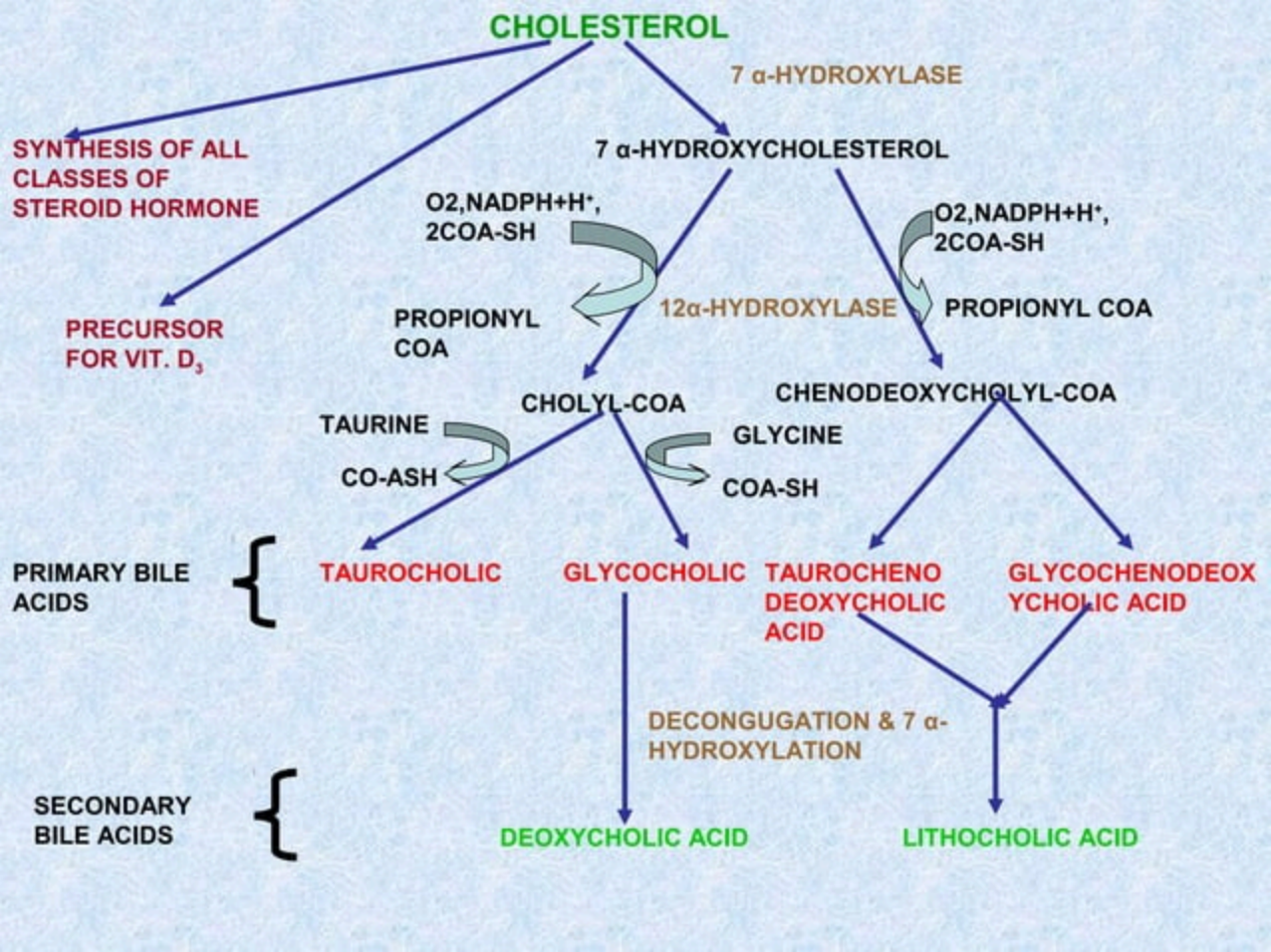
SREBP (sterol regulatory element binding protein) associated with ER membrane prot SCAP(SREBP cleavage-activating protein).

STEROL ACCELERATED ENZYME DEGRADATION(INSIGS.)

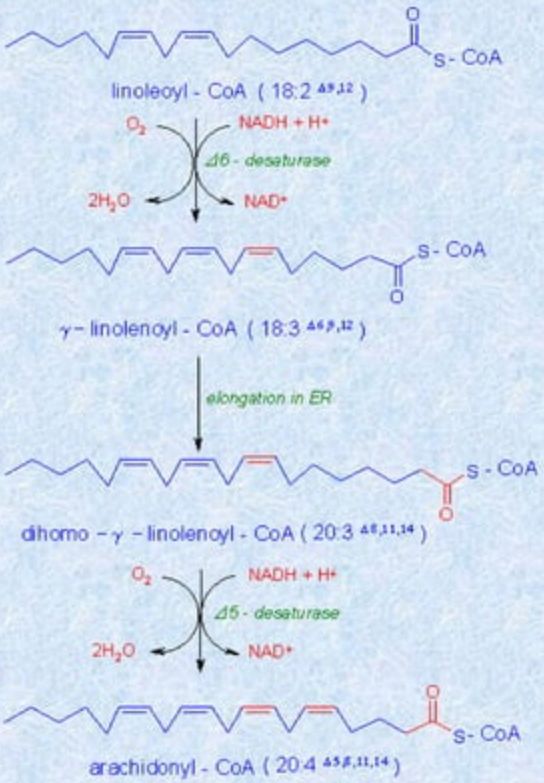
STEROL INDEPENDENT PHOSPHORYLATION-DEPHOSPHORYLATION

HORMONAL REGULATION insulin favour up-regulation

INHIBITION BY DRUGS statins


CHOLESTEROL
7 α-HYDROXYLASE
SYNTHESIS OF ALL CLASSES OF STEROID HORMONE
7 α-HYDROXYCHOLESTEROL
O2,NADPH+H+, 2COA-SH
O2,NADPH+H+, 2COA-SH
PRECURSOR FOR VIT. D3
PROPIONYL COA
12α-HYDROXYLASE
PROPIONYL COA
CHOLYL-COA
CHENODEOXYCHOLYL-COA
TAURINE
CO-ASH
GLYCINE
COA-SH
PRIMARY BILE ACIDS
TAUROCHOLIC
GLYCOCHOLIC
TAUROCHENO DEOXYCHOLIC ACID
GLYCOCHENODEOXYCHOLIC ACID
DECONGUGATION & 7 α-HYDROXYLATION
SECONDARY BILE ACIDS
DEOXYCHOLIC ACID
LITHOCHOLIC ACID

EICOSANOIDS



The **eicosanoids** are a group of compounds derived from 20-carbon unsaturated fatty acids **arachidonic acid**

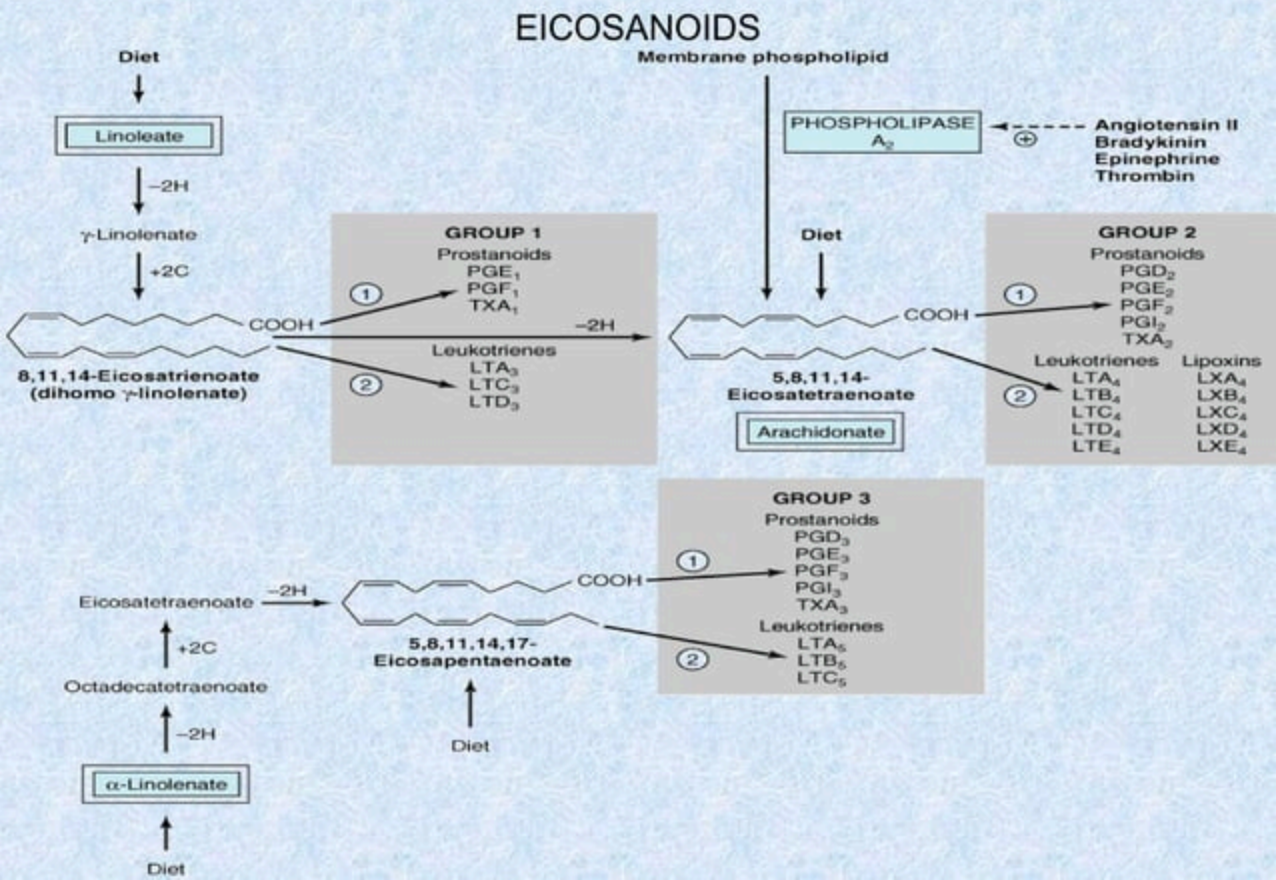
Minor eicosanoids are derived from dihomo-γ-linoleic acid and eicosopentaenoic acid (eicosanoic acids) and synthesized throughout the body.

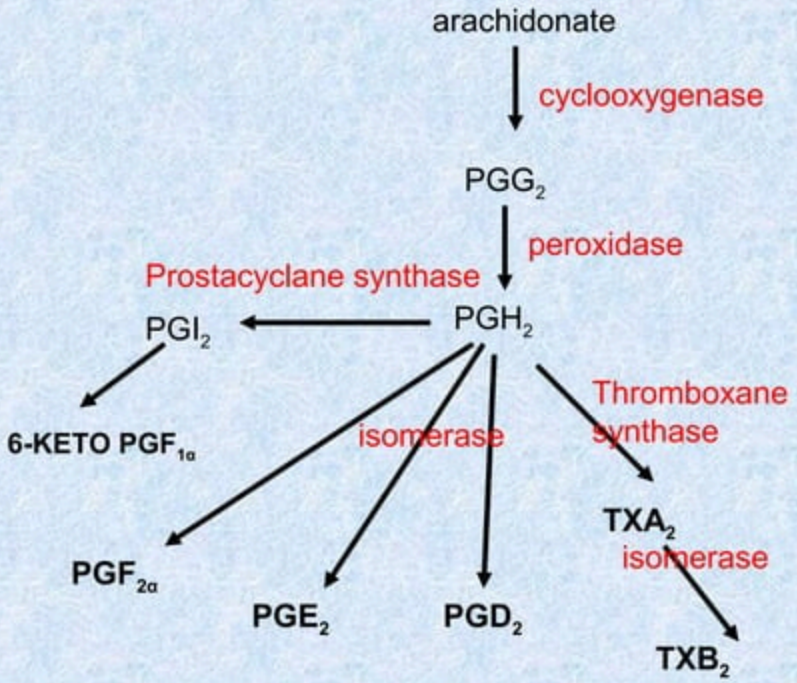
They function as short-lived chemical messengers that act near their points of synthesis ("local hormones").

The immediate dietary precursor of arachidonate is linoleate.

Within the cell, it resides predominantly at the C-2 position of membrane phospholipids and is released from there upon the activation of *phospholipase A2*

classification



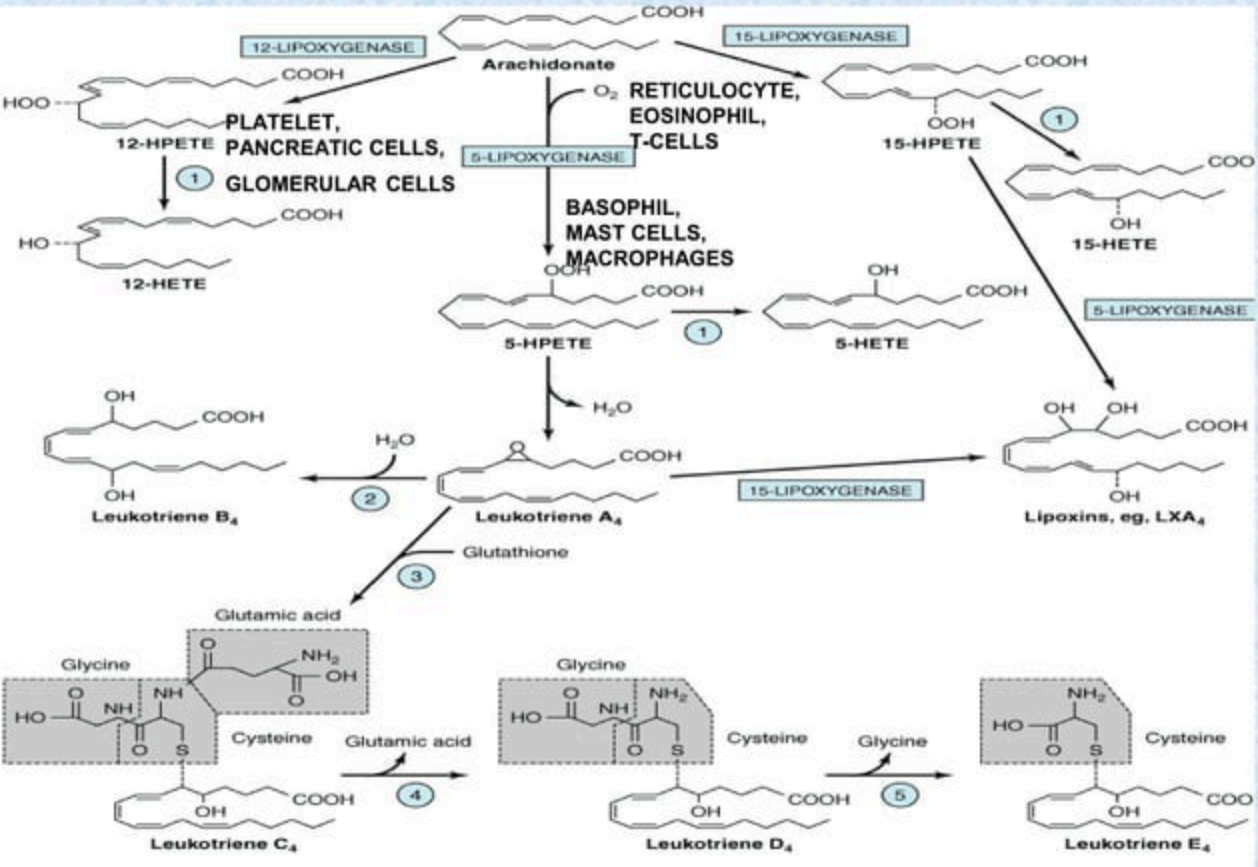


Cyclooxygenase or prostaglandin H synthase(COX1-COX2)PEROXIDASE activity.

Cox-suicide enzyme

Cyclooxygenase pathway

LIPOXYGENASE PATHWAY

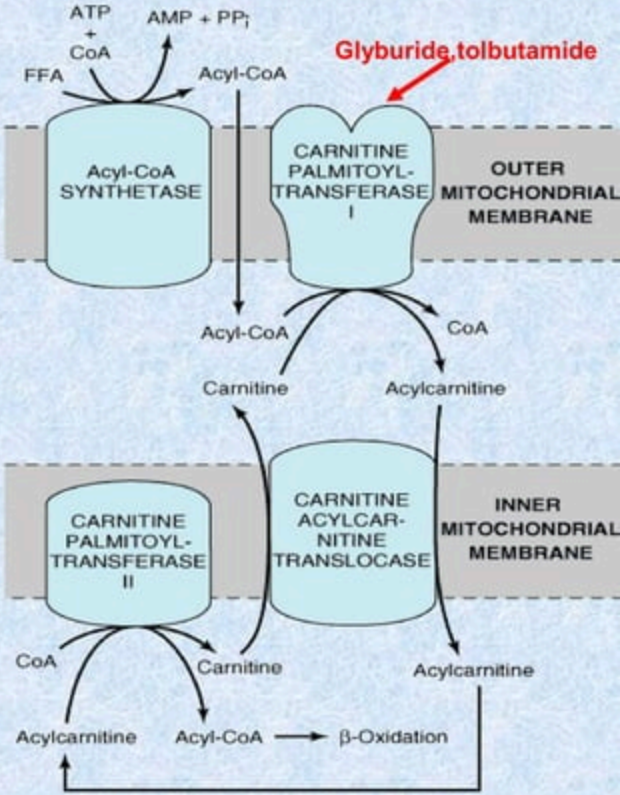


OXIDATION OF FATTY ACID

Acyl-CoA synthetases are found in the endoplasmic reticulum, peroxisomes, and inside and on the outer membrane of mitochondria.

β-hydroxy- -trimethylammonium butyrate or carnitine(SYN. LYSINE & METHIONINE)

impairment in fatty acid oxidation leads to **hypoglycemia.**



-OXIDATION OF FATTY ACIDS INVOLVES SUCCESSIVE CLEAVAGE WITH RELEASE OF ACETYL-COA

fatty acid oxidase

Generation of FADH2 & NADH

Oxidation of Fatty Acids Produces a Large Quantity of ATP

ATP PRODUCTION

1FADH2—2ATP

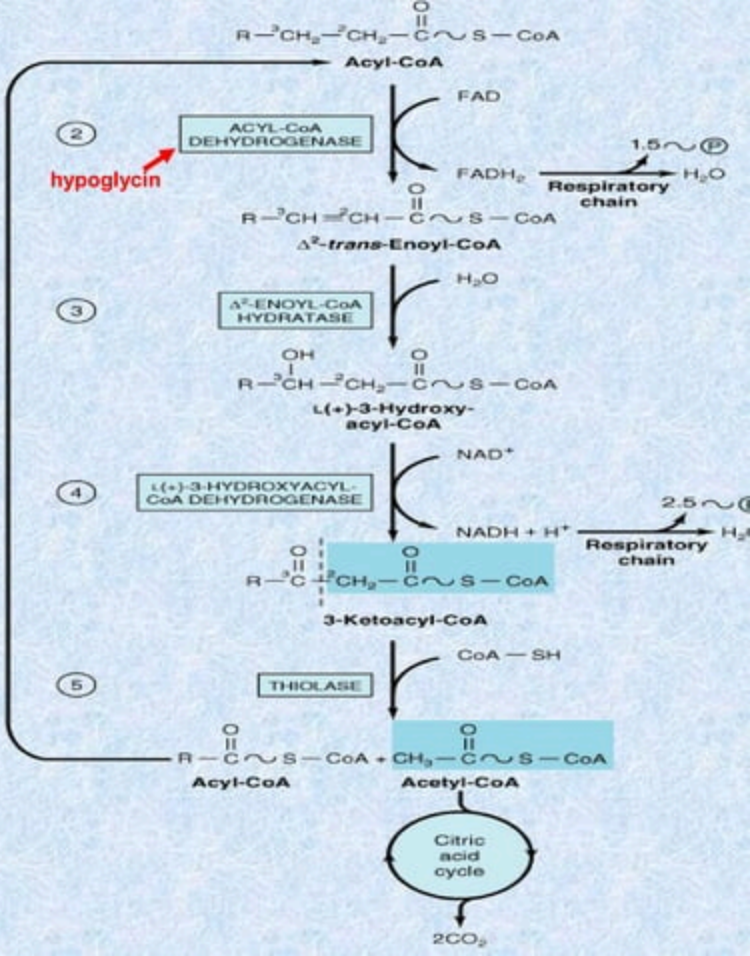
1NADH--- 3ATP

net 5(7x5=35)

ACETYL COA—TCA—12ATP. (12x8=96)

UTILISATION—2ATP.

Eg palmitic acid(16 c)7 cycles,8 acetylcoA(35+96-2=129 ATP)



Oxidation of a Fatty Acid with an Odd Number of Carbon Atoms Yields Acetyl-CoA Plus a Molecule of Propionyl-CoA

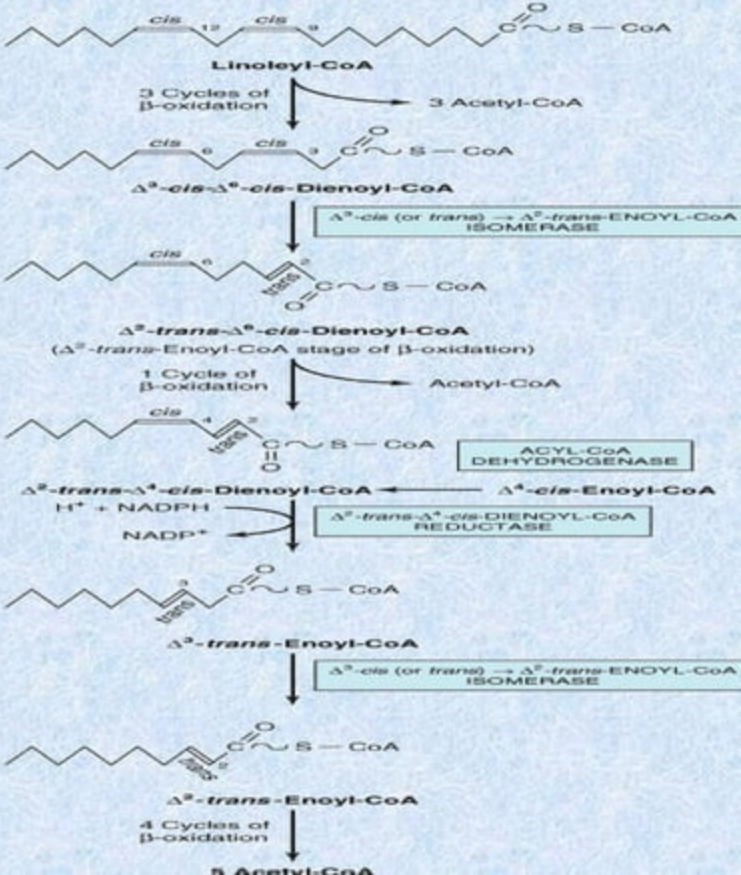
compound is converted to **succinyl-CoA**
propionyl residue from an odd-chain fatty acid is the only part of a fatty acid that is glucogenic.

Peroxisomes Oxidize Very Long Chain Fatty Acids (C20, C22)

leads to the formation of acetyl-CoA and H_2O_2 (FAD linked dh)
Dehydrogenation not linked directly to phosphorylation and the generation of ATP
Enzymes induced by **high-fat diets** and by **hypolipidemic** drugs such as **clofibrate**.
β -oxidation sequence ends at octanoyl-CoA
shorten the side chain of cholesterol in bile acid formation
Peroxisomes also take part in the synthesis of glycerolipids ,cholesterol, and dolichol

OXIDATION OF UNSATURATED FATTY ACIDS OCCURS BY A MODIFIED β -OXIDATION PATHWAY

NADPH for the dienoyl-CoA reductase step is supplied by intramitochondrial sources such as glutamate dehydrogenase, isocitrate dehydrogenase, and NAD(P)H transhydrogenase.



ketogenesis

~In liver

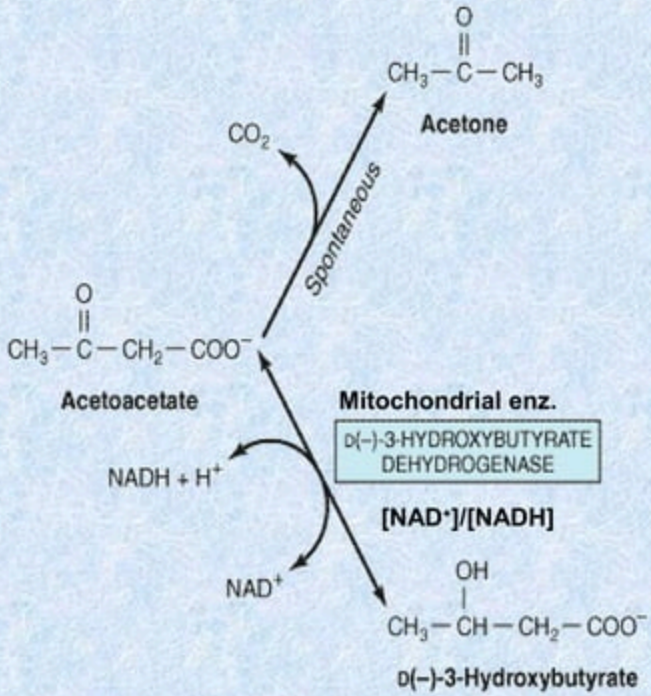
~When there is high rate of fatty acid oxidation

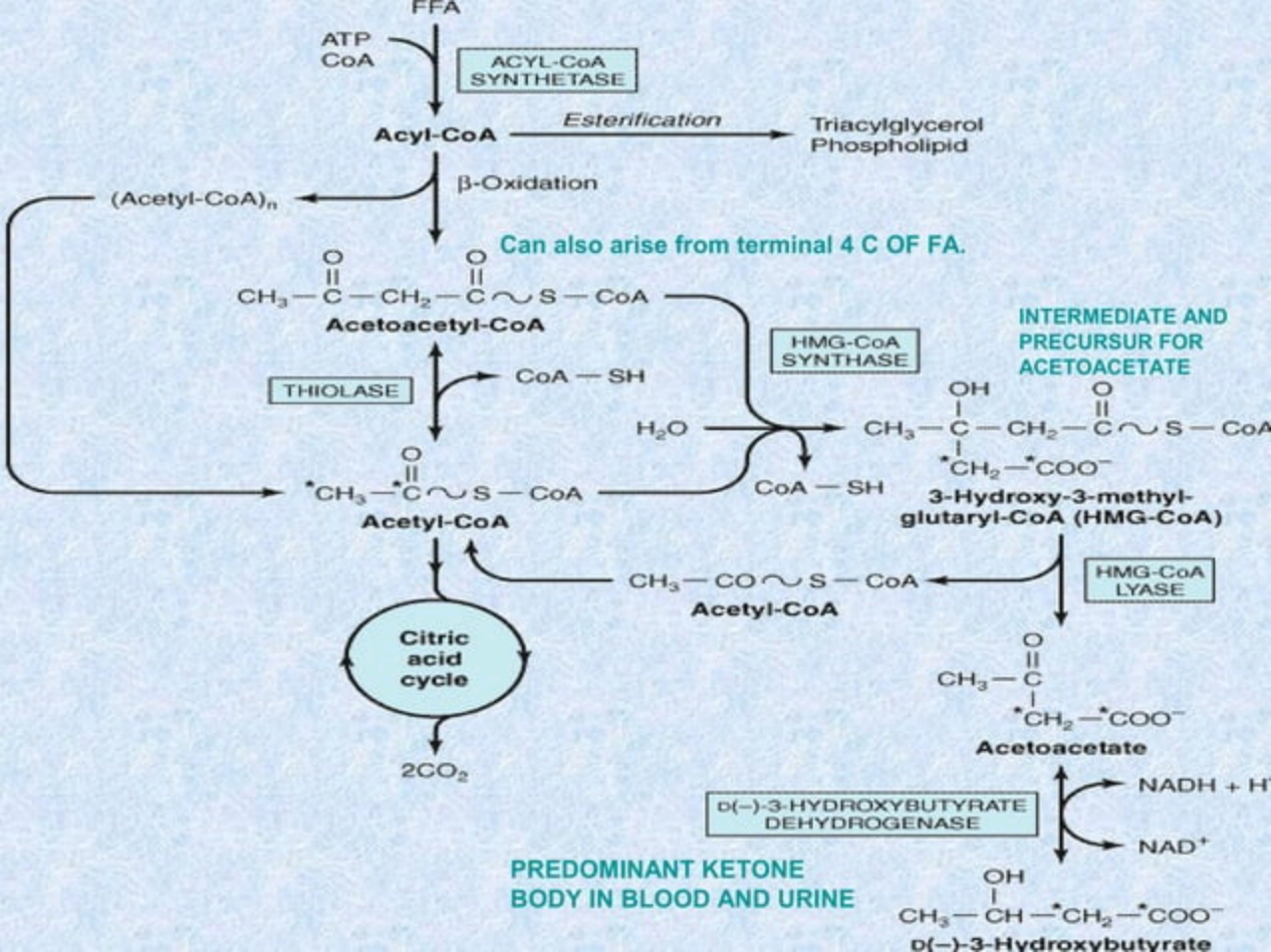
~Used as respiratory substrate by extrahepatic tissue

~Normal level 1mg/dl.

~In starvation ketone bodies is utilised by brain and heart;but liver utilises amino acid.

~Heart always FA.




FFA
ATP
CoA
ACYL-CoA SYNTHETASE
Acyl-CoA
Esterification
Triacylglycerol
Phospholipid
β-Oxidation
(Acetyl-CoA)n
Can also arise from terminal 4 C OF FA.
Acetoacetyl-CoA
THIOLASE
CoA — SH
HMG-CoA SYNTHASE
INTERMEDIATE AND PRECURSUR FOR ACETOACETATE
H2O
CoA — SH
3-Hydroxy-3-methyl-glutaryl-CoA (HMG-CoA)
Acetyl-CoA
Acetyl-CoA
HMG-CoA LYASE
Citric acid cycle
2CO2
Acetoacetate
D(−)-3-HYDROXYBUTYRATE DEHYDROGENASE
NADH + H+
NAD+
PREDOMINANT KETONE BODY IN BLOOD AND URINE
D(−)-3-Hydroxybutyrate

~Acetocetate once formed cannot be reactivated except in cytosol (cholesterol syn.)

~Increased blood level ,increased oxidation.

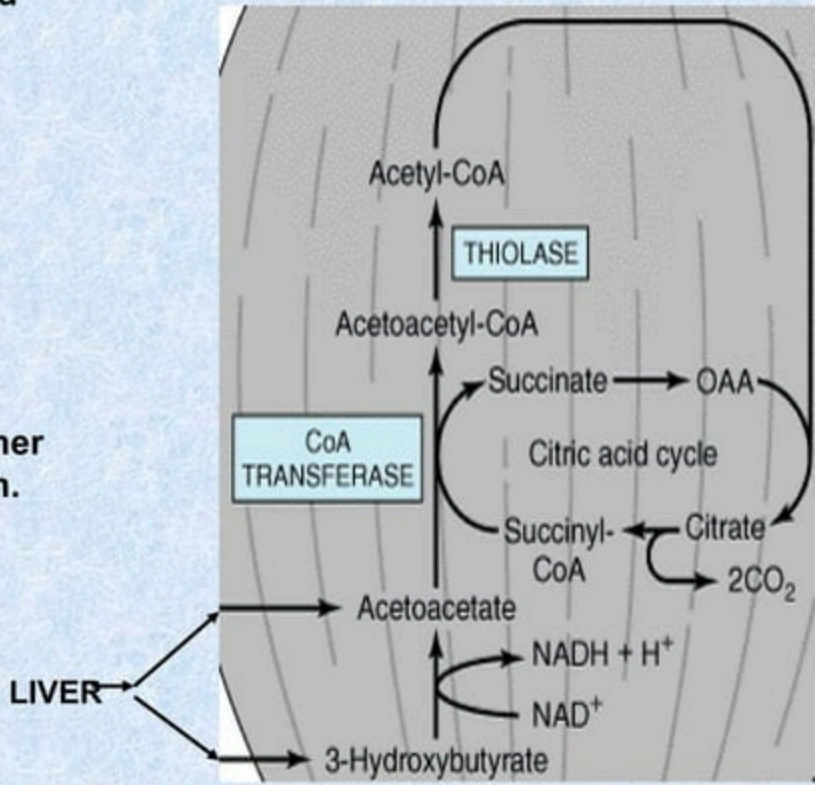
~Saturation of oxidative machinary 12mmol/l

~Ketonemia is due to increased production rather than decreased utilisation.

~Acetone is volatile.

~Severity of ketosis,mesurment of ketonemia not ketonuria.

~Rotheras test.



Regulation of ketogenesis

~Adipose tissue lipolysis.

~CPT-1—activity low in well fed state as there is increase in insulin/glucagon ratio.

~Liver oxidises FFA when increased within constraints of oxidative phosphorylation by ketone body production

Carnitine deficiency; hypoglycemia,lipid accumulation,muscular weakness.oral supplementation required.

CPT-1 deficiency: reduced fatty skeletalacid oxidation, ketogenesis, hypoglycemia.

CPT-II deficiency affects primarily skeletal muscle

Inherited defects of enzymes of β-oxidation & ketogenesis leads to non ketotic hypoglysemia, fatty liver.

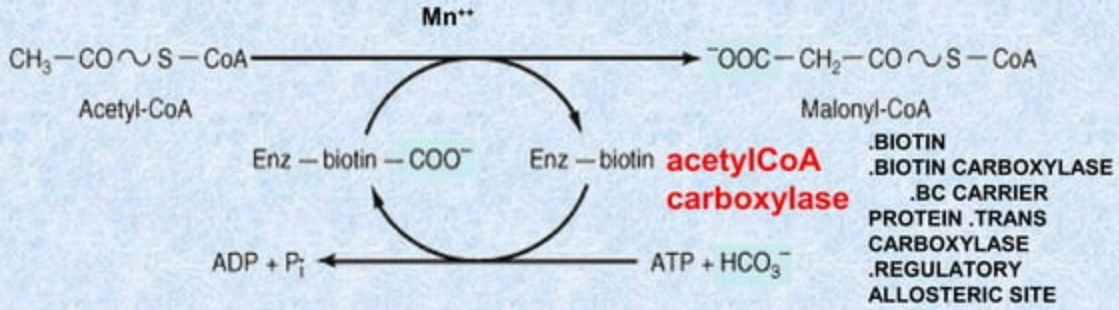
Dicarboxylic aciduria— deficiency of medium chain acylcoA DH.

FATTY ACID BIOSYNTHESIS

occurs primarily in the **cytoplasm** of :
liver
adipose (fat)
central nervous system
lactating mammary gland

• Intermediates covalently linked to acyl carrier protein
• Activation of each acetyl CoA.
• acetyl CoA + CO_2 □ Malonyl CoA
• Four-step repeating cycle, extension by 2-carbons /cycle
– Condensation
– Reduction
– Dehydration
– reduction
The enzymes of fatty acid synthesis are packaged together in a complex called as fatty acid synthase (FAS).
• The product of FAS action is palmitic acid. (16:0).
• Modifications of this primary FA leads to other longer (and shorter) FA and unsaturated FA.
• The fatty acid molecule is synthesized 2 carbons at a time• FA synthesis begins from the methyl end and proceeds
toward the carboxylic acid end.

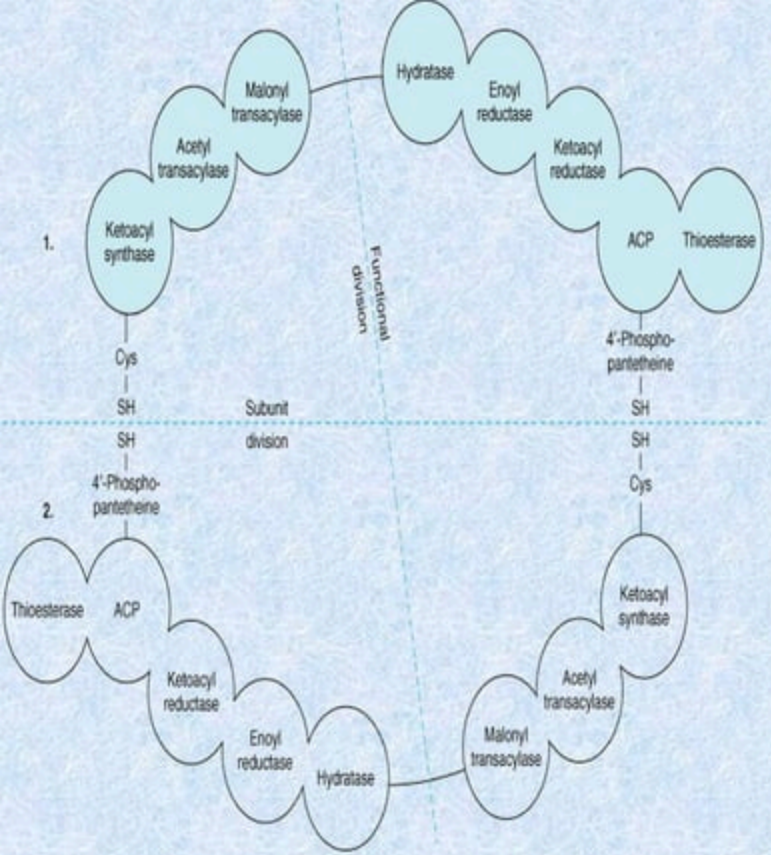
PRODUCTION OF MALONYL COA:REGULATORY,IRREVERSIBLE



For fatty acid biosynthesis, acetylCoA has to be transported from the mitochondria to the cytoplasm. This is done via a shuttle system called the **Citrate Shuttle**.

Malonyl CoA is synthesized by the action of acetylCoA carboxylase. Biotin is a required cofactor.

AcetylCoA carboxylase is under allosteric regulation. Citrate is a positive effector and palmitoyl CoA is a negative effector



homodimeric enzyme, seven catalytic activities, and eight sites two carriers

ACP1 acts as a holding station for acetyl- or fatty acyl- groups.

ACP2, binds the growing fatty acyl chain during the condensation and reduction

Net reaction: Acetyl CoA + 7 malonyl CoA + 14 NADPH + 14 H+ □ Palmitate + 7 CO_2 + 8 CoA + 14 $NADP^+$ + $6H_2O$

Source: Murray RK, Granner DK, Rodwell VW: *Harper's Illustrated Biochemistry*, 27th Edition: http://www.accessmedicine.com

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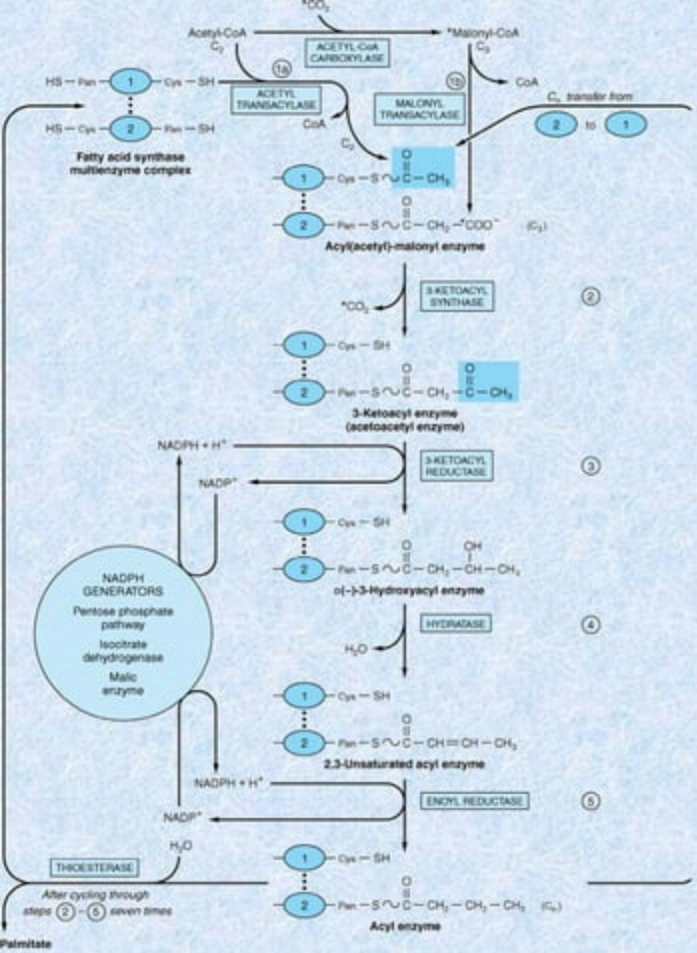

Acetyl-CoA:ACP transacylase, transfers an acetyl group to cysteinyl-S on ACP1.

malonyl-group transferred to the pantetheinyl-S of ACP2 by **Malonyl-CoA:ACP transacylase**.

carbon dioxide leaves the malonyl group, with the electrons from its bond attacking the acyl group on ACP1 **(Ketoacyl-ACP synthase)**

β-ketoacyl group ready to go through the reverse of the reactions of β-oxidation. Thus the keto-group is reduced to an alcohol using NADPH **(β-ketoacyl-ACP reductase)**,

followed by the elimination of the alcohol **(Enoyl-ACP hydrase)** to give the *cis*-2,3-enoyl group.

The enoyl is then reduced with NADPH substituting for FADH2 **(Enoyl-ACP reductase)** to give the saturated acyl group.

Finally the acyl group is transferred from the pantotheinyl-S of ACP2 to the cysteinyl-S on ACP1 **(ACP-acyltransferase)** leaving ACP2 available to pick up the next malonyl moiety.

After seven turns of the cycle palmitate is released.