Metabolism: Other Lipids

Sugars are the building blocks of carbohydrates, amino acids are the building blocks of proteins and nucleotides are the building blocks of the nucleic acids - DNA and RNA. Another crucial building block is acetyl-CoA, which is used to build many lipid substances, including fatty acids, cholesterol, fat soluble vitamins, steroid hormones, prostaglandins, endocannabinoids, and the bile acids. Indeed, acetyl-CoA goes into more different classes of molecule than any other building block.

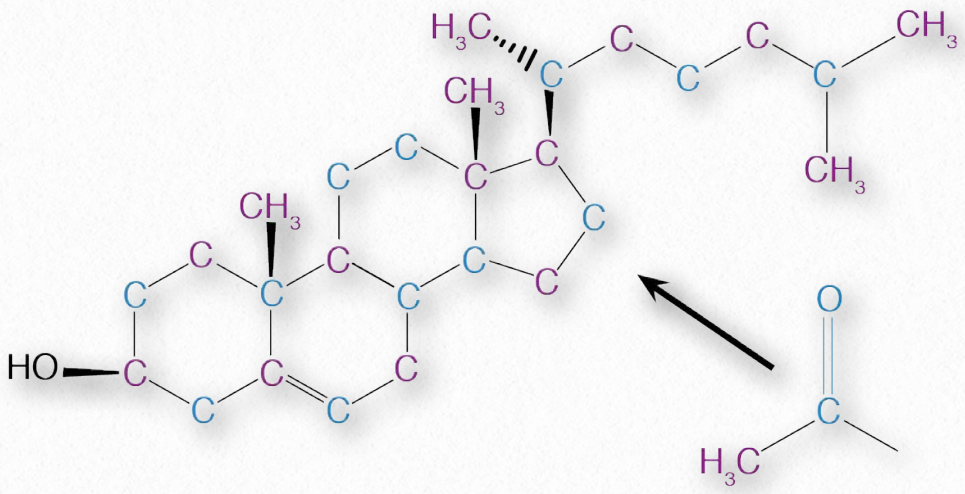


Figure 6.110 - Acetyl-CoA's carbons mapped onto cholesterol

Image by Penelope Irving

Mevalonate pathway

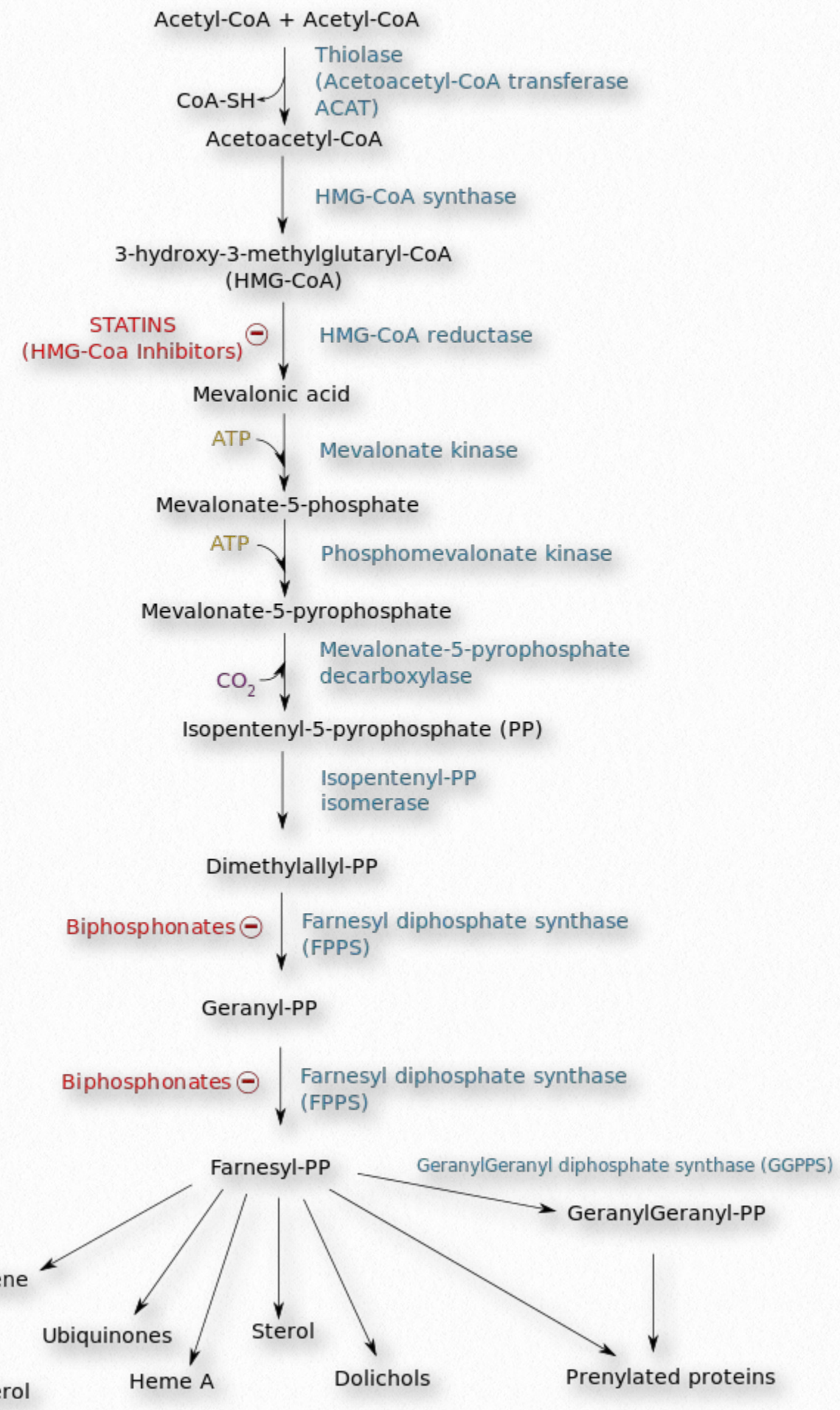


Figure 6.111 - Synthesis of isoprenoids from acetyl-CoA

Isoprenoids

We focus our attention here on a group of molecules made from acetyl-CoA that are known as as the isoprenoids. Isoprenoids are a large, diverse and ancient group of molecules that are found in all three domains of life. As noted earlier, they are components of membrane lipids in the cell membranes of archaebacteria, but beyond this, they serve an astonishing variety of functions. From photosynthetic pigments to plant defense compounds, from flavor compounds in cinnamon, mint, ginger and cloves to plant and animal hormones, from the cannabinoids in marijuana to the lycopene that gives tomatoes their color, and from heme to the quinones in the electron transport chain, isoprenoids are ubiquitous in cells. Isoprenoids derive their name from the fact that they are, in fact, made from five carbon building blocks called isoprenes that are derived from acetyl-CoA. The synthesis of the two isoprene units - isopentenyl pyrophosphate and dimethylallyl pyrophosphate is shown in Figure 6.111 and Figure 6.112.

YouTube Lectures by Kevin HERE & HERE

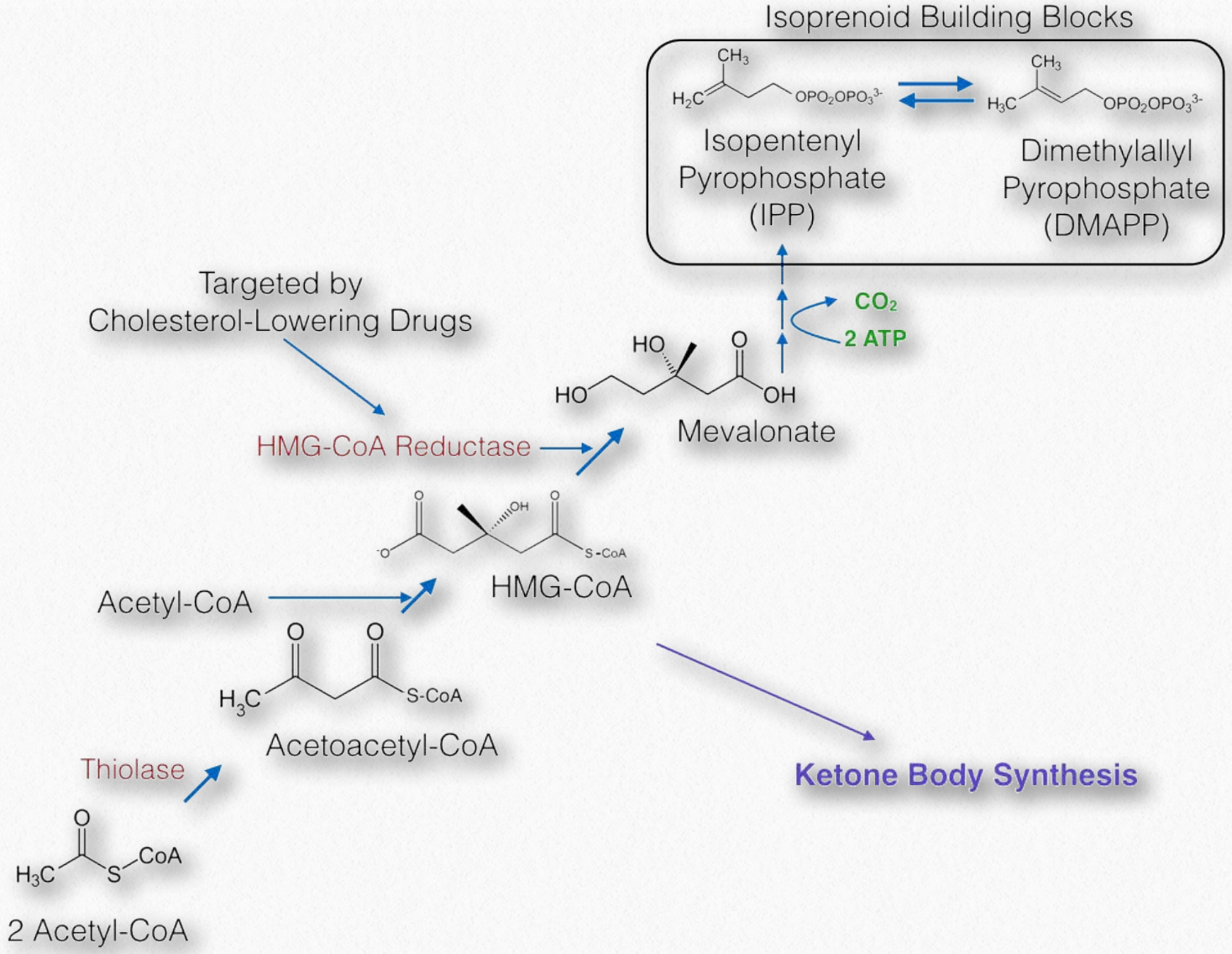


Figure 6.112 - Reactions to make isoprenes from acetyl-CoA

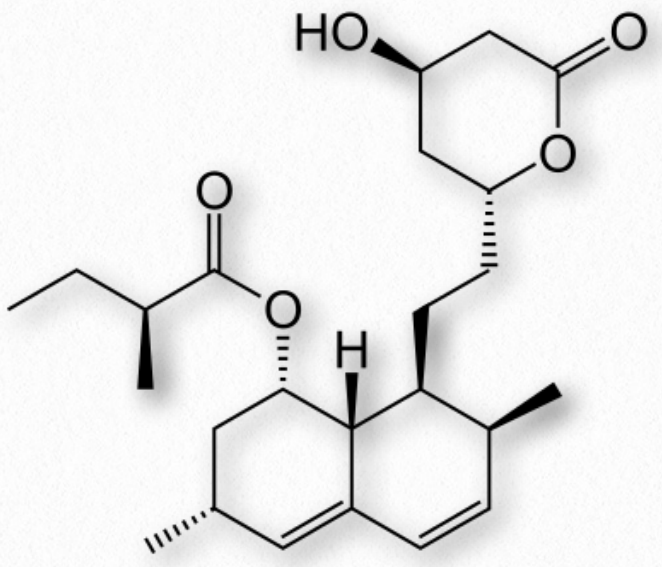


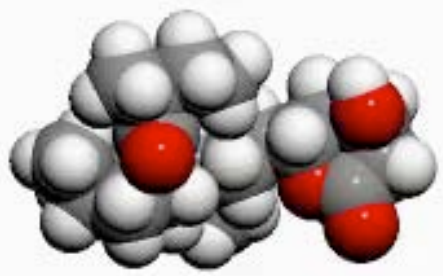
Figure 6.113 - Lovastatin

Wikipedia

The pathway leading up to isoprene synthesis overlaps with that of ketone body synthesis, for the two reactions (Figure 6.112), as has been discussed earlier in this book (see HERE). Thiolase catalyzes the initial reaction, joining together two acetyl-CoA molecules to make acetoacetyl-CoA. In the second reaction catalyzed by HMG-CoA synthase, a third acetyl-CoA is joined to form the six carbon compound known as hydroxymethyl glutaryl-CoA (HMG-CoA). Reaction three is an important one biologically and medically because of the enzyme catalyzing it - HMG-CoA reductase.

Statins

Medically, HMG-CoA reductase is the target of a class of drugs known as statins (Figure 6.113 & Movie 6.1), which are used to reduce cholesterol levels in people. These competitive inhibitors, which compete with HMG-CoA for binding have two effects. First, they reduce the production of mevalonate, which restricts the amount of substrate available to make cholesterol. Second, and perhaps more importantly, they increase production of LDL receptors in the liver, which favors uptake and destruction of LDLs, thus lowering serum cholesterol levels.



Movie 6.1 - Lovastatin

Wikipedia

Regulation

Biologically, the HMG-CoA reductase enzyme is also of importance because it is the primary regulatory point in cholesterol synthesis. Control of it is complex. First, it is feedback inhibited by cholesterol itself. High levels of glucose in the blood activate the enzyme. Phosphorylation by AMP-activated protein kinase inhibits its activity. Interestingly, the same enzyme phosphorylates and inactivates acetyl-CoA carboxylase - the only regulatory enzyme controlling fatty acid synthesis. Transcription of the gene encoding HMG-CoA reductase

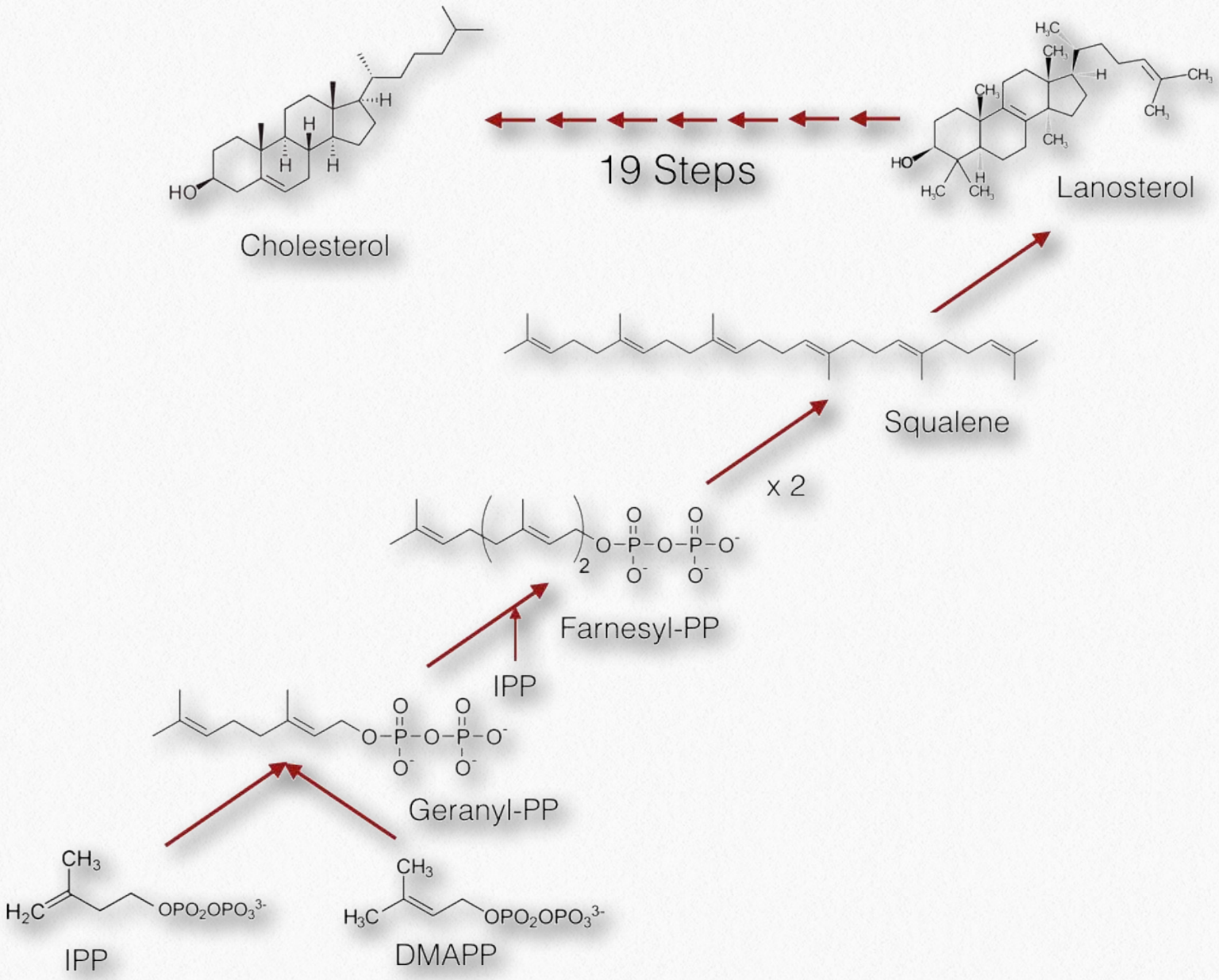


Figure 6.114 - Synthesis of cholesterol from isoprene units - isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP)

is enhanced by binding of the sterol regulatory element binding protein (SREBP) to the sterol recognition element (SRE) located near the gene coding sequence. As cholesterol levels rise, SREBP is proteolytically cleaved and transcription stops.

From HMG-CoA, the enzyme HMG-CoA reductase catalyzes the formation of mevalonate. This reaction requires NADPH and results in release of coenzyme A. Mevalonate gets phosphorylated twice and then decarboxylated to yield the five carbon intermediate known as isopentenyl-pyrophosphate (IPP). IPP is readily converted to the other important isoprenoid unit, dimethylallylpyrophosphate (DMAPP).

Isoprenes

These two five carbon compounds, IPP and DMAPP, are also called isoprenes (Figure 6.115) and are the building blocks for the syn-

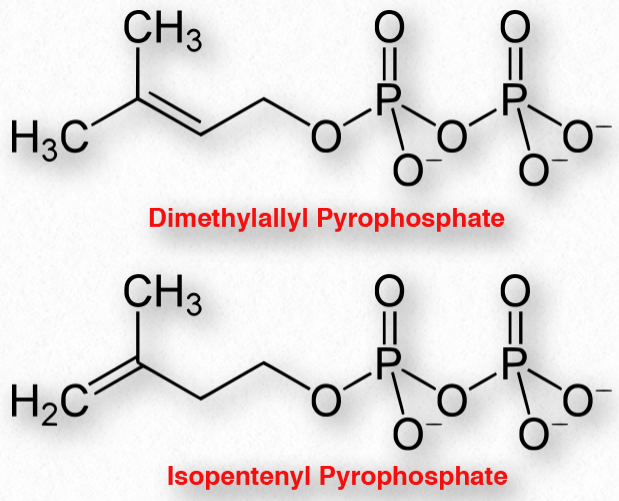


Figure 6.115 - Isoprene building blocks

thesis of cholesterol and related compounds. This pathway proceeds in the direction of cholesterol starting with the joining of IPP and DMAPP to form geranyl-pyrophosphate. Geranyl-pyrophosphate combines with another IPP to make farnesyl-pyrophosphate, a 15-carbon compound.

Squalene

Two farnesyl-pyrophosphates join to create the 30-carbon compound known as squalene. Squalene, in a complicated rearrangement involving reduction and molecular oxygen forms a cyclic intermediate known as lanosterol (Figure 6.116) that resembles cholesterol. Conversion of lanosterol to cholesterol is a lengthy process involving 19 steps that occur in the endoplasmic reticulum.

The cholesterol biosynthesis pathway from lanosterol is a long one and requires significant amounts of reductive and ATP energy. As noted earlier (see HERE), cholesterol has

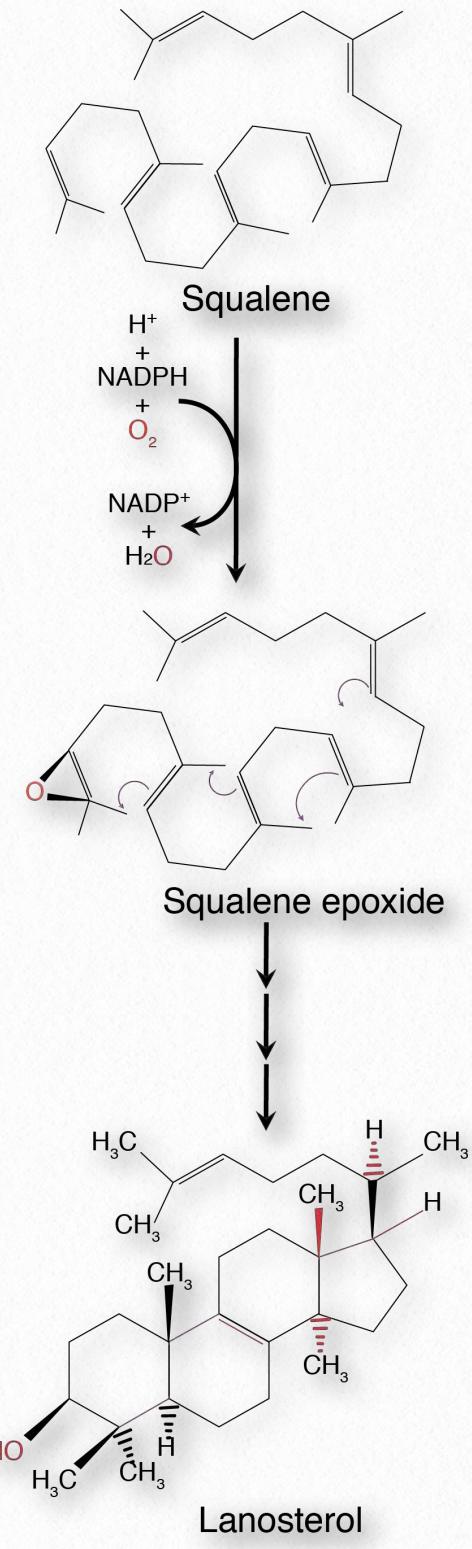


Figure 6.116 - Synthesis of lanosterol from squalene

Image by Penelope Irving

an important role in membranes. It is also a precursor of steroid hormones and bile acids and its immediate metabolic precursor, 7-dehydrocholesterol (Figure 6.117), branches to form vitamin D (Figure 6.118).

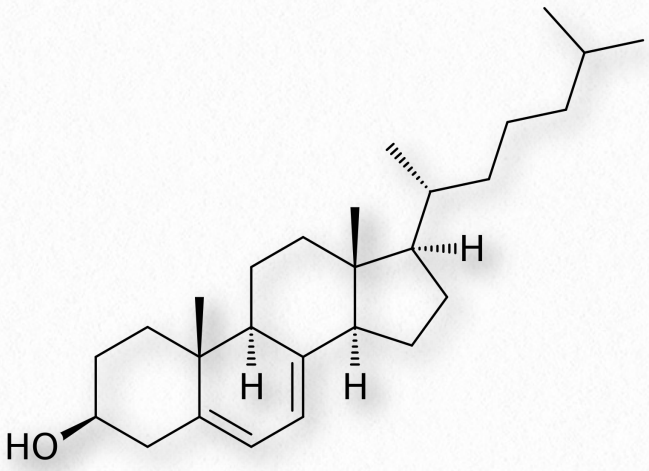
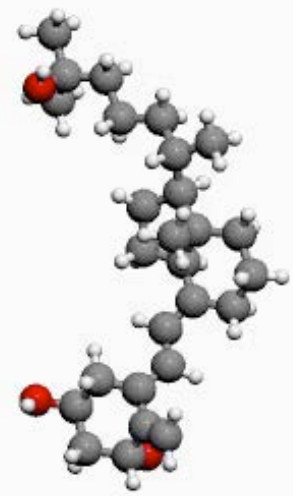


Figure 6.117 - 7-Dehydrocholesterol - A precursor of cholesterol and vitamin D

All steroid hormones in animals are made from cholesterol and include the progestagens, androgens, estrogens, mineralocorticoids, and the glucocorticoids. The branch molecule for all of the steroid hormones is the cholesterol metabolite (and progestagen) known as pregnenalone (Figure 6.119). The progestagens are thus precursors of all of the other classes of steroid hormones.



Movie 6.2 - Calcitriol - The active form of vitamin D

Wikipedia

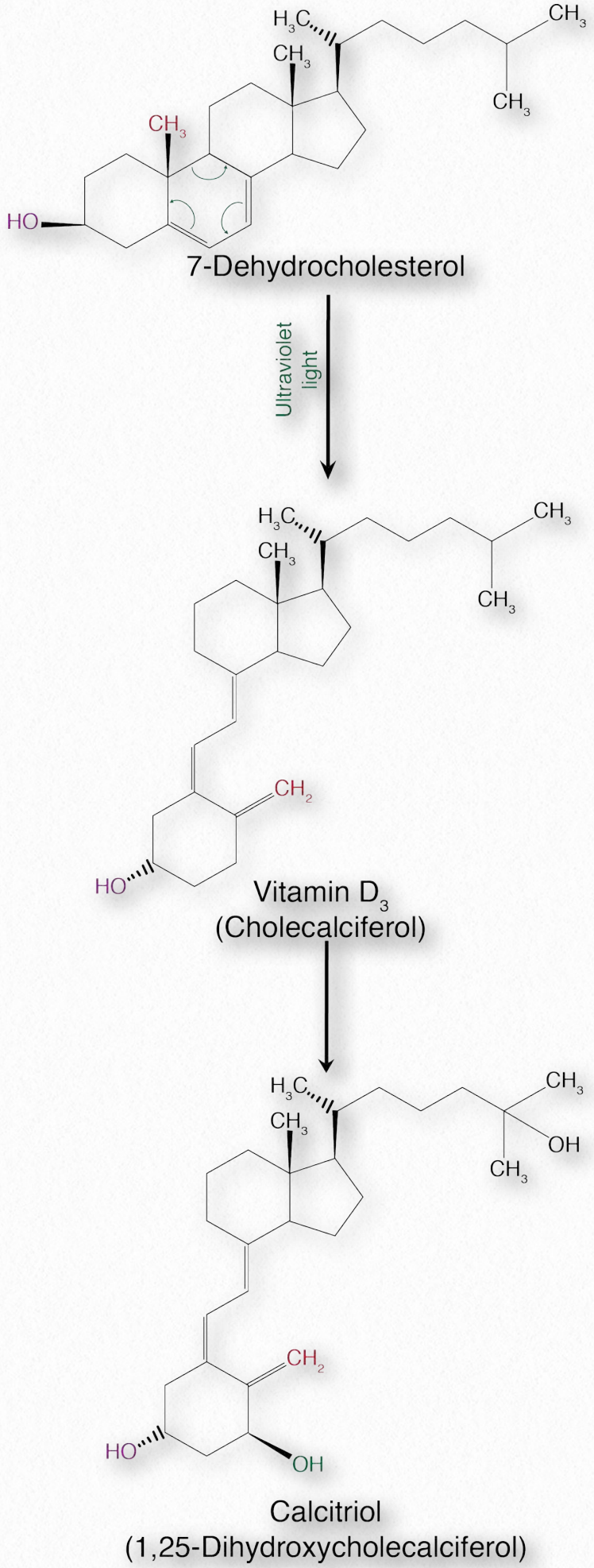


Figure 6.118 - Synthesis of the active form of vitamin D

Image by Penelope Irving

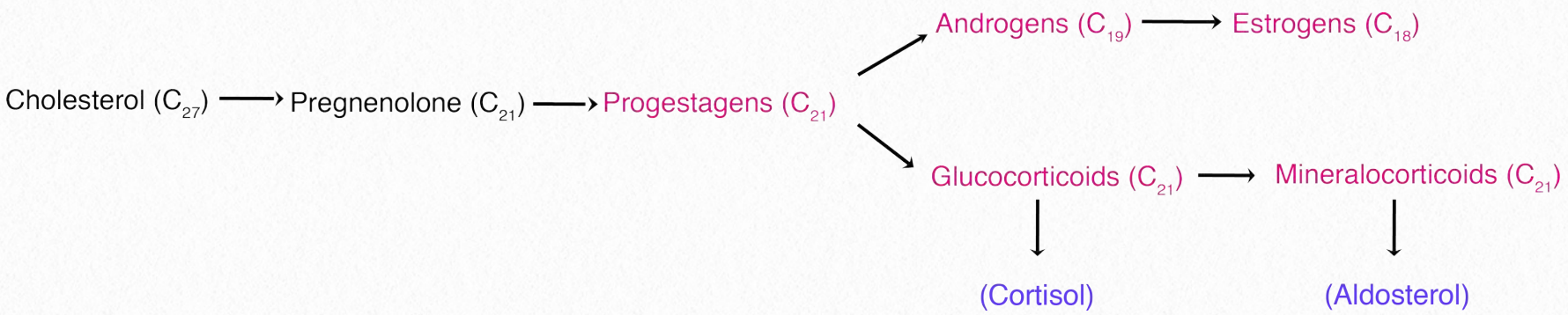


Figure 6.119 - Synthesis of steroid hormones from cholesterol. Example glucocorticoids and mineralocorticoids shown in blue.

Image by Penelope Irving

The estrogens are derived from the androgens in an interesting reaction that required formation of an aromatic ring (Figure 6.120). The enzyme catalyzing this reaction is known as an aromatase and it is of medical significance. The growth of some tumors is stimulated by estrogens, so aromatase inhibitors are prescribed to prevent the formation of estrogens and slow tumor growth. Two commonly used inhibitors include exemestane (a suicide inhibitor - Figure 6.121) and anastrozole (a competitive inhibitor).

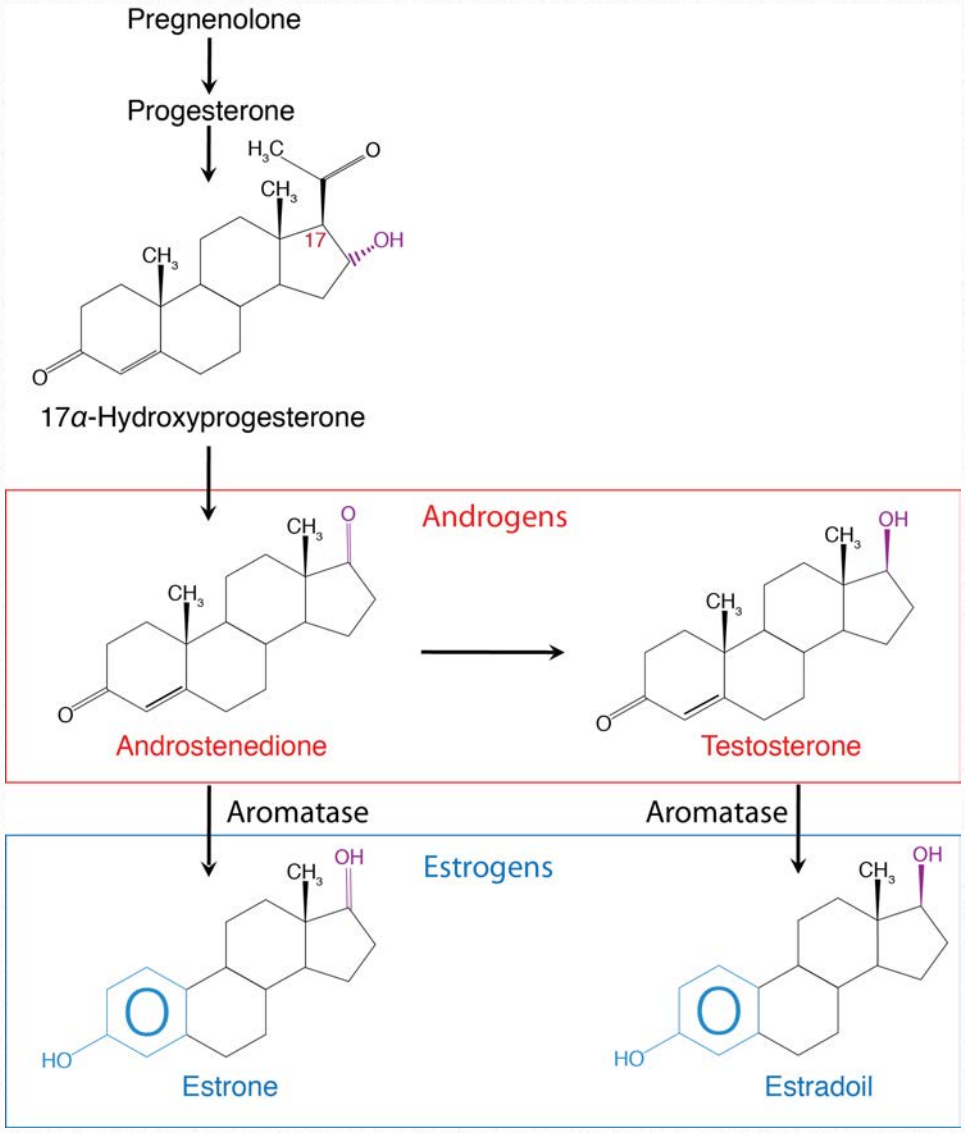


Figure 6.120 - Synthesis of Estrogens from Androgens

Image by Penelope Irving

Other fat-soluble vitamins

Synthesis of other fat soluble vitamins and chlorophyll also branches from the isoprenoid synthesis pathway at geranyl pyrophosphate. Joining of two geranylgeranyl pyrophosphates oc-

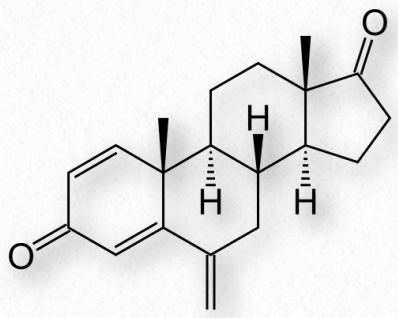


Figure 6.121 - Exemestane - A suicide inhibitor of aromatase

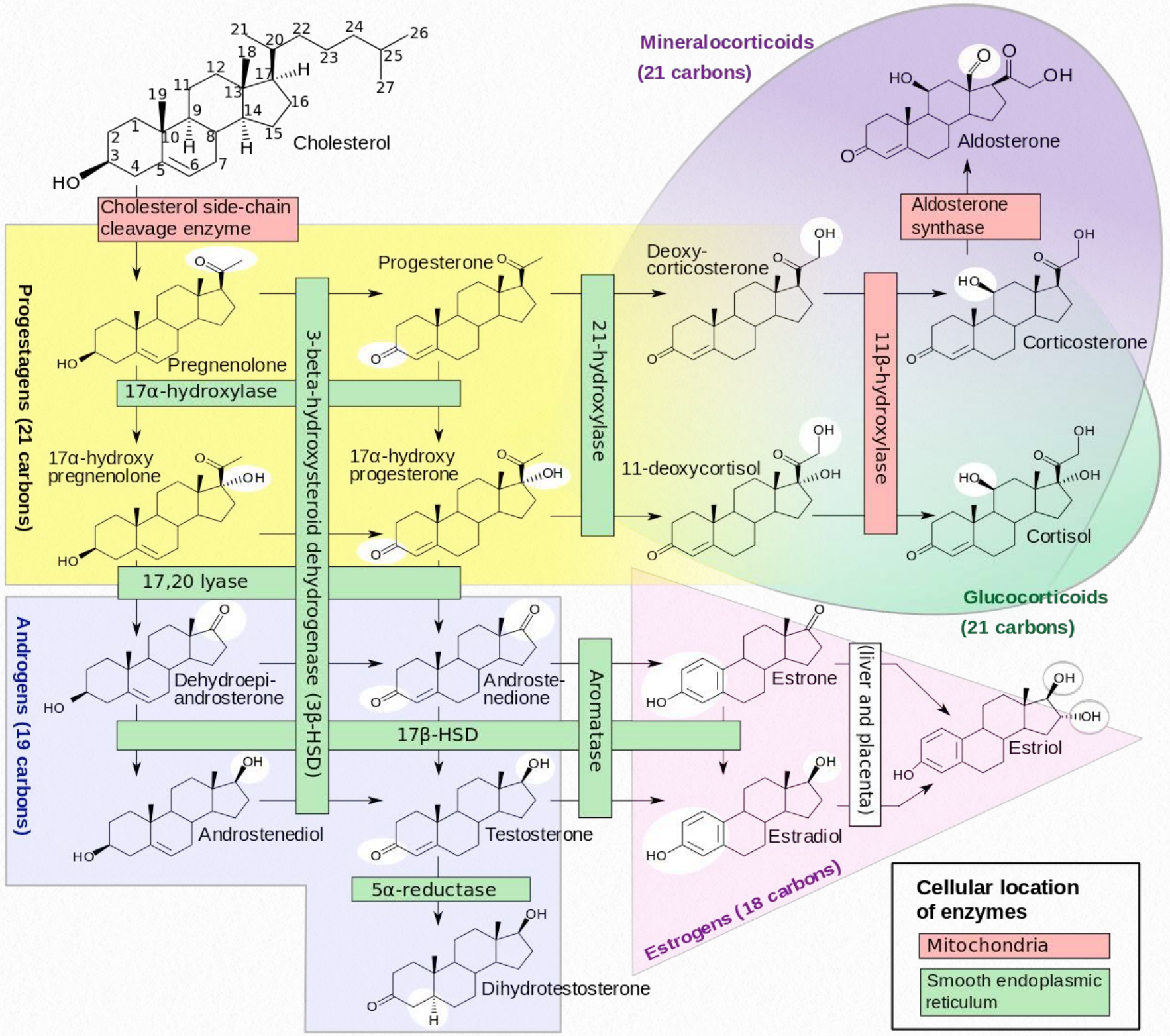


Figure 6.122 - Synthesis of steroid hormones from cholesterol

Wikipedia

curs in plants and bacteria and leads to synthesis of lycopene, which, in turn is a precursor of β-carotene, the final precursor of Vitamin A (see below also). Vitamins E and K, as well as chlorophyll are all also synthesized from geranylgeranyl pyrophosphate.

YouTube Lectures by Kevin HERE & HERE

Bile acid metabolism

Another metabolic pathway from cholesterol leads to the polar bile acids, which are important for the solubilization of dietary fat

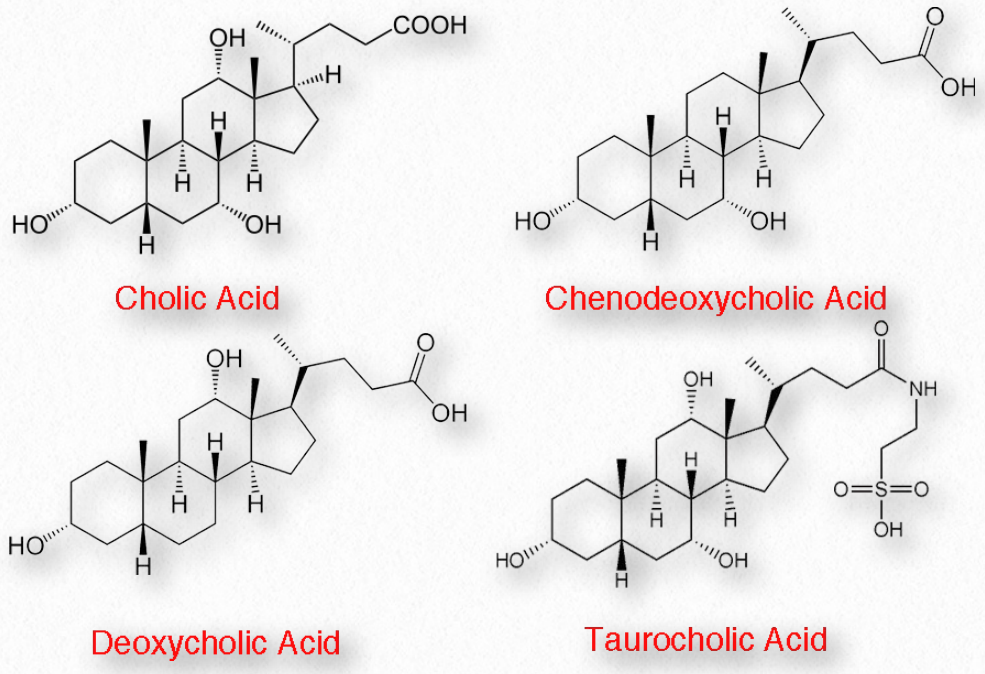


Figure 6.123 - Four bile acids

during digestion. Converting the very non-polar cholesterol to a bile acid involves oxidation of the terminal carbon on the side chain off the rings. Other alterations to increase the polarity of these compounds include hydroxylation of the rings and linkage to other polar compounds.

Common bile acids include cholic acid, chenodeoxycholic acid, glycocholic acid, taurocholic acid, and deoxycholic acid (Figure 6.123). Another important consideration about bile acids is that their synthesis reduces the amount of cholesterol available and promotes uptake of LDLs by the liver. Normally bile acids are recycled efficiently resulting in limited reduction of cholesterol levels. However, inhibitors of the recycling promote reduction of cholesterol levels.

Vitamin A Synthesis

Vitamin A is important for many cellular functions related to growth, differentiation and organogenesis during embryonic development, tissue maintenance, and vision, to name a few.

There are three main active forms of the vitamin, retinal, retinol and retinoic acid, each with its own set of functions. Retinal, complexed with the protein, opsin, is found in the rod cells of the retina and is necessary for vision. Retinol and retinoic acid both function as signaling molecules that can modulate gene expression during development.

Synthesis of vitamin A occurs as a branch in synthesis of isoprenoids. Addition of isopentenyl pyrophosphate to farnesyl pyrophosphate creates a 20-carbon intermediate, geranylgeranyl pyrophosphate (GGPP - Figure 6.124).

Joining of two GGPPs creates a 40 carbon intermediate that is unstable and decomposes to phytoene. Desaturases oxidize two single bonds in phytoene, creating lycopene.

Lycopene is a linear 40 carbon unsaturated molecule found in tomatoes and other red vegetables and it gives them their color. Cyclization of end portions of lycopene give rise to β-carotene, the precursor of vitamin A (retinal/retinol - Figure 6.124).

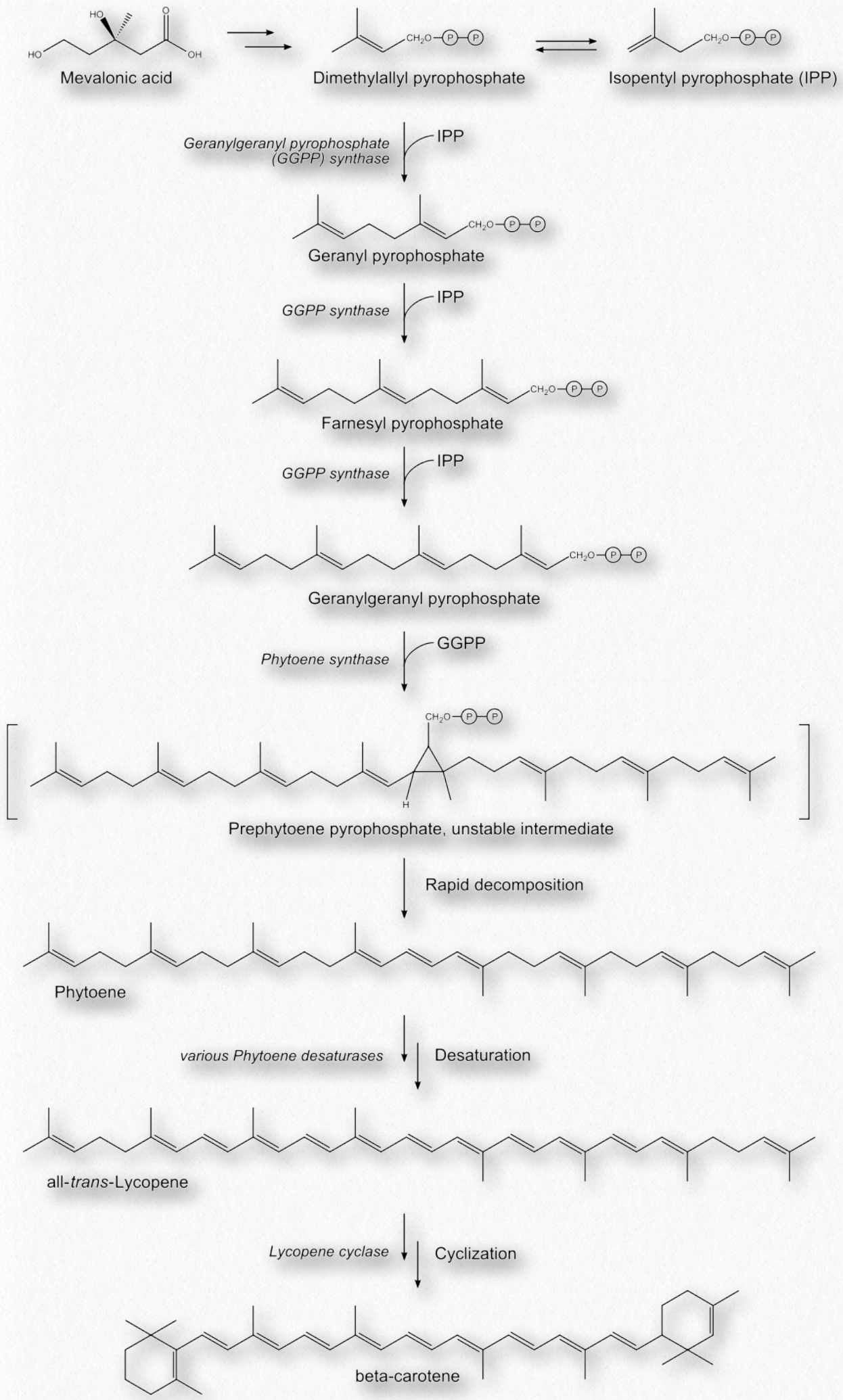


Figure 6.124 - Synthesis of β-carotene from mevalonate

Wikipedia

β-carotene is found in carrots and other orange vegetables, and is converted in the body to vitamin A. Catalytic action by β-Carotene 15,15' monooxygenase cleaves β-carotene to form retinal (the aldehyde form used in vision).

The enzyme retinol dehydrogenase catalyzes reduction of retinal to retinol (storage form). Oxidation of retinal creates another important retinoid known as retinoic acid. This form of vitamin A cannot be reduced back to retinal and thus cannot be used for vision or storage.

Instead, retinoic acid has roles in embryonic development. Retinoic acid acts through binding to the Retinoic Acid Receptor (RAR).

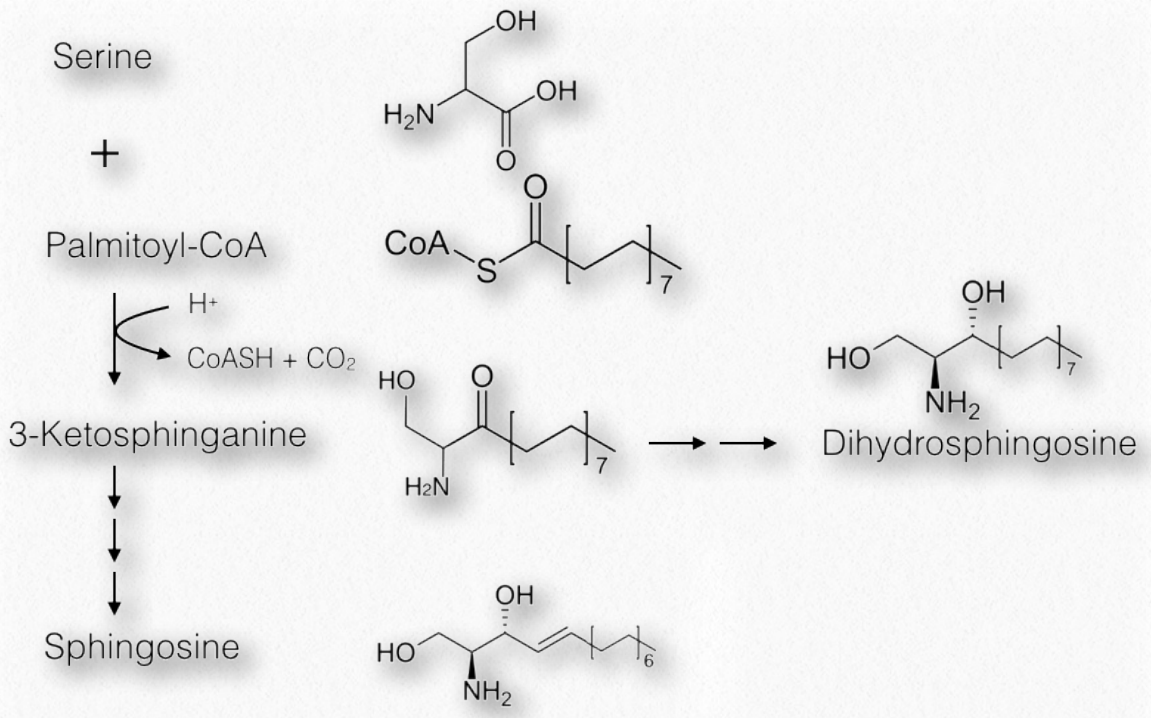


Figure 6.125 - Synthesis of dihydrosphingosine from serine and palmitoyl-CoA

RAR binds to DNA and affects transcription of several important sets of genes important for differentiation. These include the Hox genes, which control anterior/posterior patterning in early embryonic development.

Sphingolipid synthesis

Synthesis of sphingolipids, which are found primarily in brain and nerve tissue, begins with palmitoyl-CoA and serine that combine to make an 18-carbon amine called 3-keto-sphinganine (Figure 6.125). Reduction of that by NADPH yields dihydrosphingosine and addition of a fatty acid from an acyl-CoA yields N-acylsphinganine, which is a ceramide (Figure 6.126). A ceramide can be converted into a cerebroside by addition of a glucose from UDP-glucose (Figure 6.127).

If a few other simple sugars are added to the cerebroside, a globoside is created. If, instead of adding sugar, a phosphocholine is added from phosphatidylcholine, then sphingomyelin is created (Figure 6.127). If a complex set of sugars are added to to a cerebroside, then a ganglioside results (Figure 6.127).

Sphingolipid breakdown

In the overall metabolism of sphingolipids, the greatest problems arise with their catabolism. Figure 6.128 illustrates the nu-

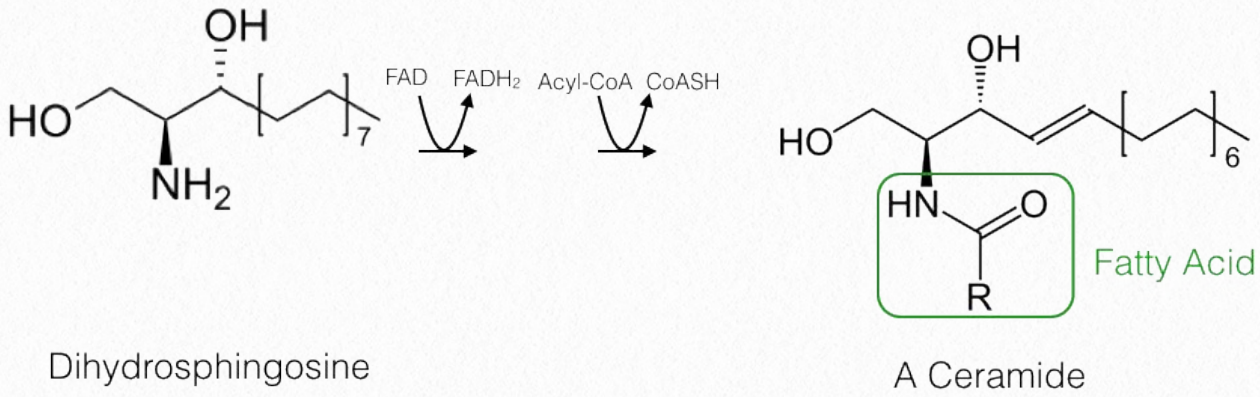


Figure 6.126 - Conversion of dihydrosphingosine to a ceramide

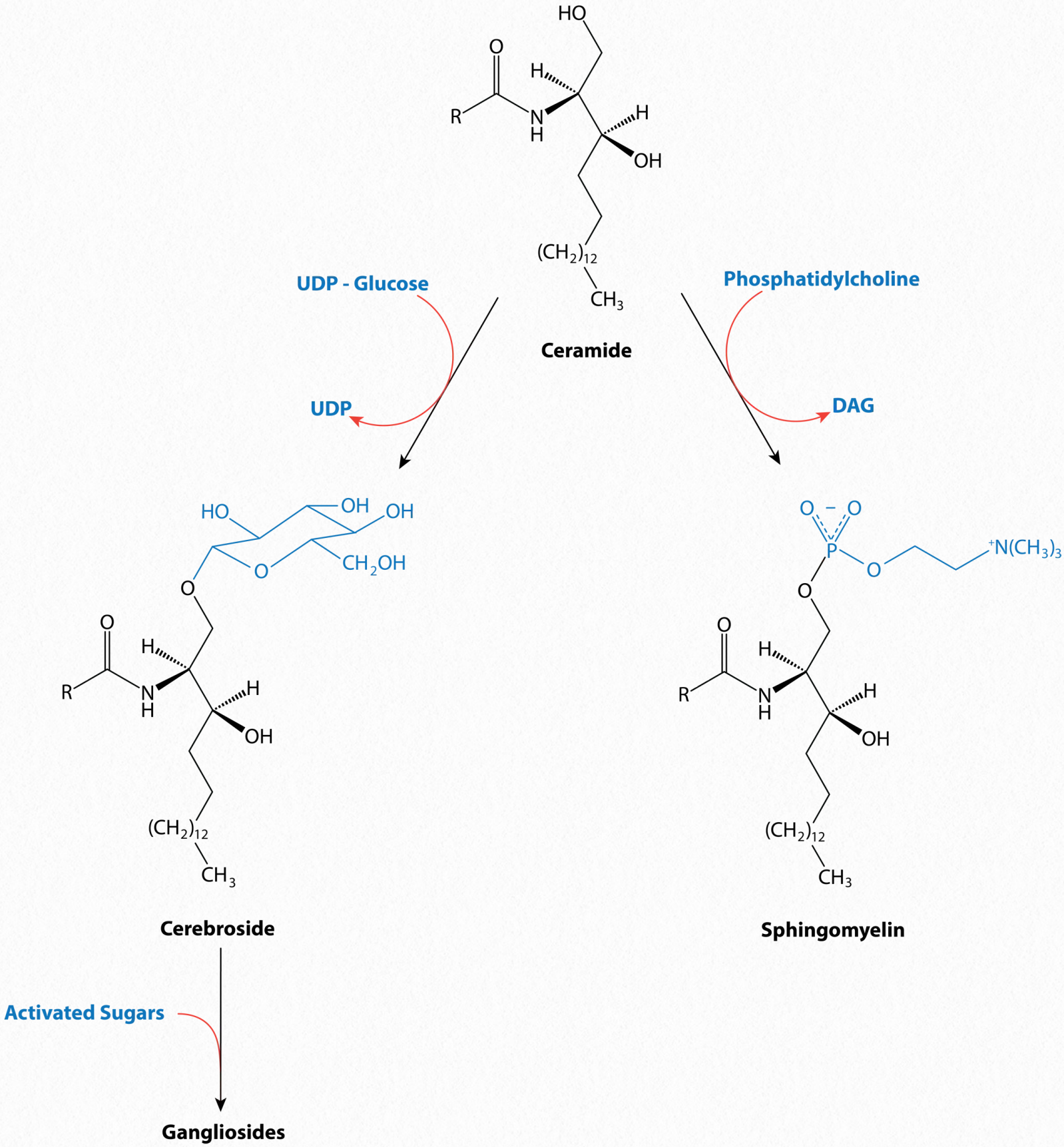


Figure 6.127 - Conversion of a ceramide into other sphingolipids

Image by Ben Carson

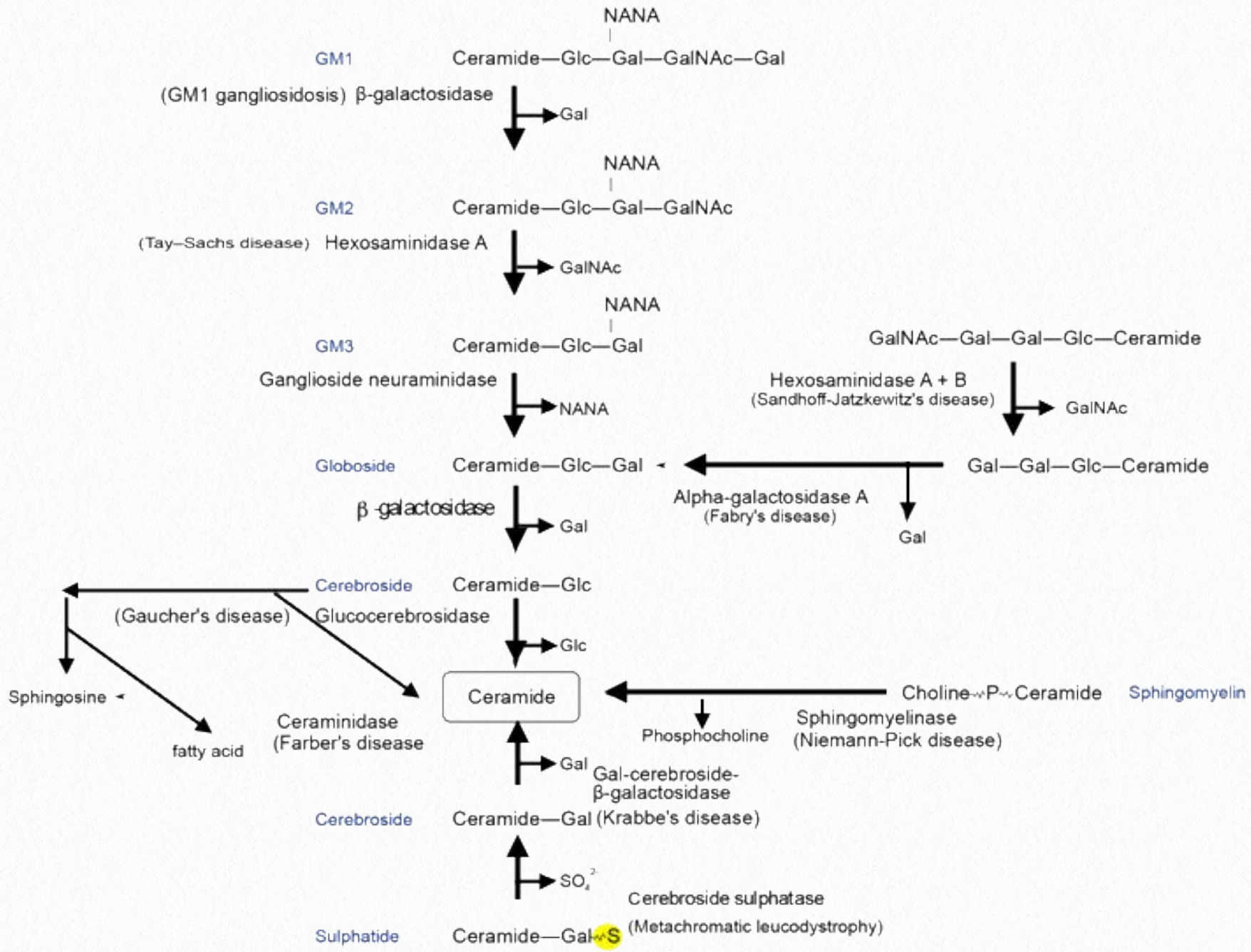


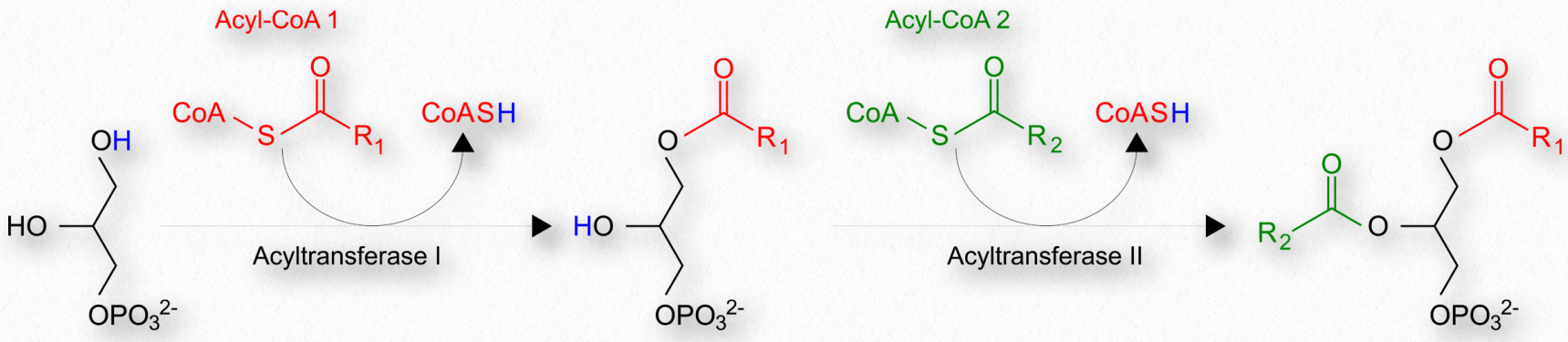
Figure 6.128 - Enzymes involved in sphingolipid breakdown and the diseases associated with their absence in parentheses. NANA = N-acetyl-neuraminic Acid / Glc = glucose / Gal = galactose / GalNAc = N-acetyl-galactosamine

Wikipedia

merous genetic diseases arising from mutations in DNA coding for some of these enzymes. All are lysosomal storage diseases and many of these are quite severe. GM1 glandiosidoses (arising from inability to breakdown GM1 gangliosides) cause severe neurodegeneration and seizures. Individuals suffering from them typically die by age 3. Tay-Sachs disease usually causes death by age 4, though late-onset forms of the disease in adults are known.

YouTube Lectures by Kevin HERE & HERE

With Gaucher's disease, three different types have been described with widely varying effects. In some, the disease is fatal by age four and in others, it does not manifest until teens



Glycerol 3-phosphate Lysophosphatidic acid Phosphatidic acid

Figure 6.129 - Phosphatidic acid synthesis

Wikipedia

or even adulthood. Fabry's disease patients can live into their 50s, on average.

Glycerophospholipid metabolism

Glycerophospholipids are the major components of membranes. Synthesis of glycerophospholipids begins with glycerol-3-phosphate. In the first reaction, glycerol-3-phosphate gains a fatty acid at position one from an acyl-CoA, followed by a duplicate reaction at position two to make phosphatidic acid (Figure 6.129). This molecule, which can branch to other reactions to form fats, is an important intermediate in the synthesis of many glycerophospholipids. Glycerophospholipid compounds can often be made by more than one pathway. The nucleotide CDP plays an important role in glycerophospholipid synthesis, serving as part of an activated intermediate for synthesis of phosphatidyl compounds. This is necessary, because formation of the phosphodiester bonds of these compounds requires higher energy input.

Cells use two strategies to accomplish this. Both involve CDP. In the first, CTP combines with phosphatidic acid to make CDP-diacylglcyerol with release of a pyrophosphate. The reaction is catalyzed by phosphatidate cytidylyltransferase.

CTP + Phosphatidic acid ⇅ **CDP-diacylglycerol + PP_i**

CDP-diacylglycerol then serves as an activated intermediate to donate the phosphotidate part of itself to another molecule. The reaction below illustrates one example

CDP-diacylglycerol + Serine ⇅ **Phosphatidylserine + CMP**

The second strategy is to make a CDP derivative of the group being added to phosphatidic acid. An example is shown next

Phosphocholine + **CTP**

⇅

CDP-choline + **PPi**

Then the CDP donates the phosphocholine to a diacylglycerol to made phosphatidylcholine and CMP

CDP-choline + **Diacylglycerol**

⇅

Phosphatidylcholine + **CMP**

Synthesis of other important glycerophospholipids follows from these basic strategies. Phosphatidylethanolamine can be easily made from phosphatidylserine by decarboxylation.

Phosphatidylserine

⇅

Phosphatidylethanolamine + **CO_2**

Phosphatidylethanolamine can serve as a precursor in an alternative pathway for making phosphatidylcholine (SAM = S-Adenosyl Methioinine / SAH = S-Adenosyl Homocysteine)

Phosphatidylethanolamine + 3 **SAM**

⇅

Phosphatidylcholine + 3 **SAH**

Phosphatidylserine and phosphatidylethanolamine can swap groups reversibly in the reaction below

Phosphatidylethanolamine + **Serine**

⇅

Phosphatidylserine + **Ethanolamine**

Similarly, phosphatidylserine and phosphatidylcholine can be interchanged as follows:

Phosphatidylserine + **Choline**

⇅

Phosphatidylcholine + **Serine**

Phosphatidylglycerol can be made from glycerol-3-phosphate and CDP-diacylglycerol

CDP-diacylglycerol + **Glycerol-3-phosphate**

⇅

Phosphatidylglycerol + **CMP**

Cardiolipin, which is essentially a diphosphatidyl compound can be made by joining CDP-diacylglyerol with phosphatidylglycerol

Phosphatidylglycerol + **CDP-diacylglycerol**

⇅

Cardiolipin + CMP

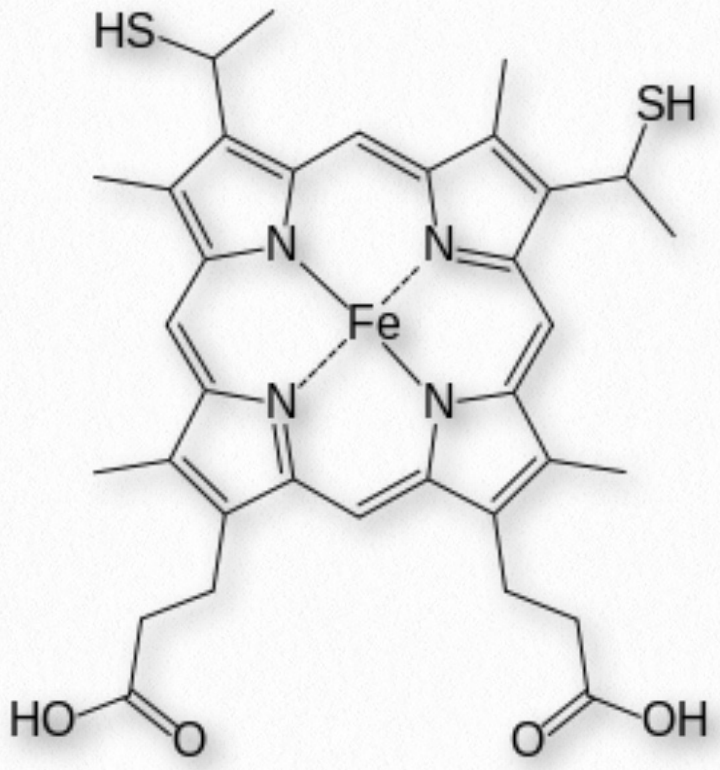


Figure 6.130 - Heme C

Phosphtidylinositol can be made from CDP-diacylglycerol and inositol.

CDP-diacylglycerol + **Inositol**

⇅

Phosphatidylinositol + **CMP**

Heme synthesis

The porphyrin ring found in the hemes of animals, fungi, and protozoa (Figure 6.130) is synthesized starting from very simple compounds (Figure 6.131). The process is a bit complicated, occurring between the cytoplasm and the mitochondrion. The first step is the creation of δ-aminolevulinic acid (also called aminolevulinic acid or dALA) from glycine and Succinyl-CoA.

Glycine + **Succinyl-CoA**

⇅

δ-aminolevulinic acid

Joining of two δ-aminolevulinic acid molecules together with splitting out of two molecules of water yields porphobilinogen.

2 **δ-aminolevulinic acid**

⇅

Porphobilinogen + $2H_2O$

Joining of four molecules of porphobilinogen together yields hydroxylmethylbilane (Figure 6.132).

4 **Porphobilinogen**

⇅

Hydroxymethylbilane

Next, a series of reactions involving 1) loss of water; 2) loss of four molecules of carbon dioxide; 3) loss of two more carbon dioxides, loss of six protons and electrons and (finally) 4) addition of Fe^{++} with loss of two protons yields heme. Individual heme molecules may be further processed.

Two enzymes in heme synthesis are sensitive to the presence of lead, and this is one of the primary causes of lead toxicity in humans. Inhibition of the enzymes leads to 1) anemia and 2) accumulation of δ-aminolevulinic acid,

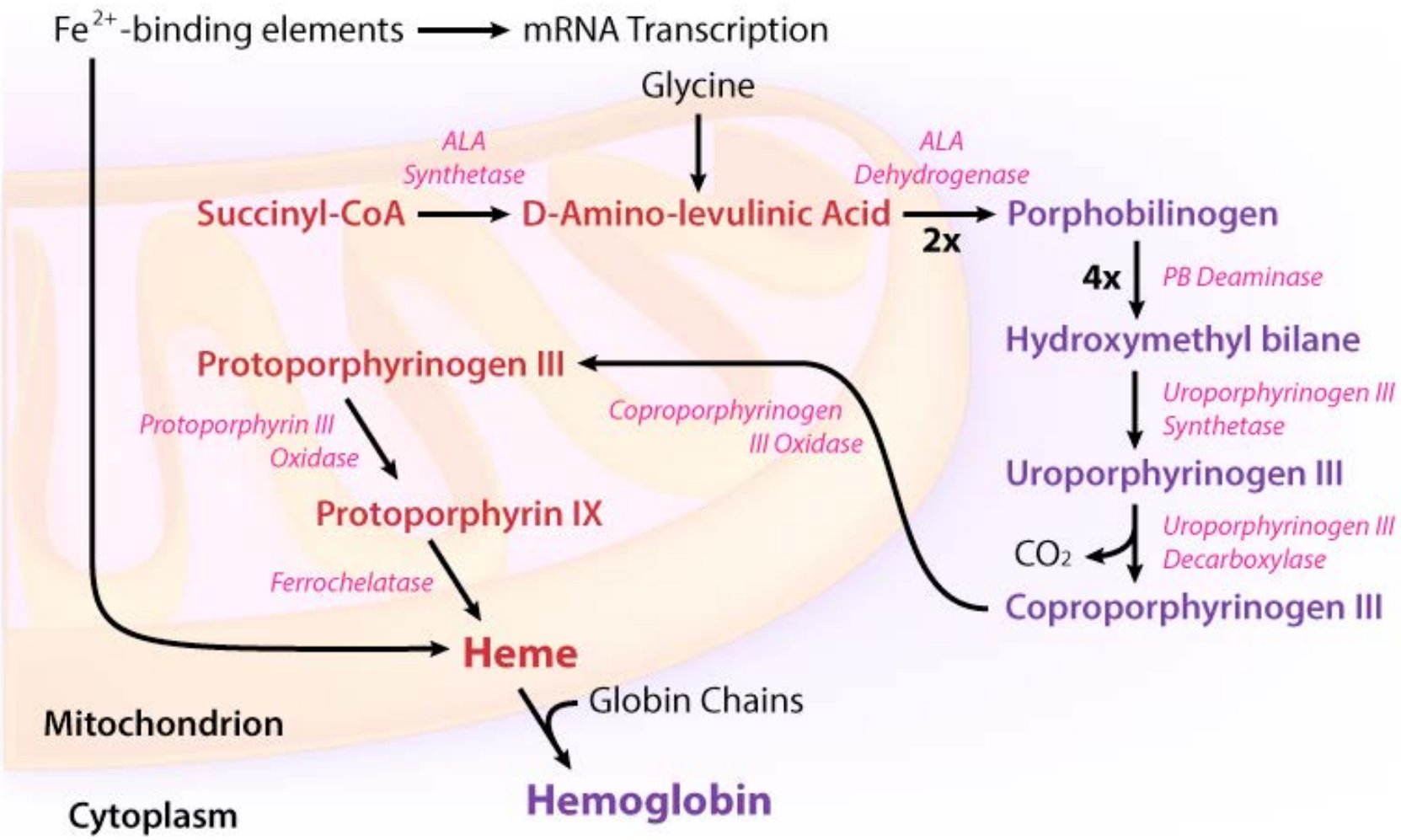


Figure 6.131 - Heme synthesis

Image by Aleia Kim

which can be harmful to neurons in development, resulting in learning deficiencies in children.

Porphyria

Defects in enzymes of the pathway can also lead to porphyrias, diseases in which one or more of the intermediates in the heme synthesis pathway accumulate due to deficiency of the enzyme necessary to convert the accumulating material into the next molecule in the pathway. The accumulation of purplish intermediates gave the diseases the name porphyria from the Greek word for purple.

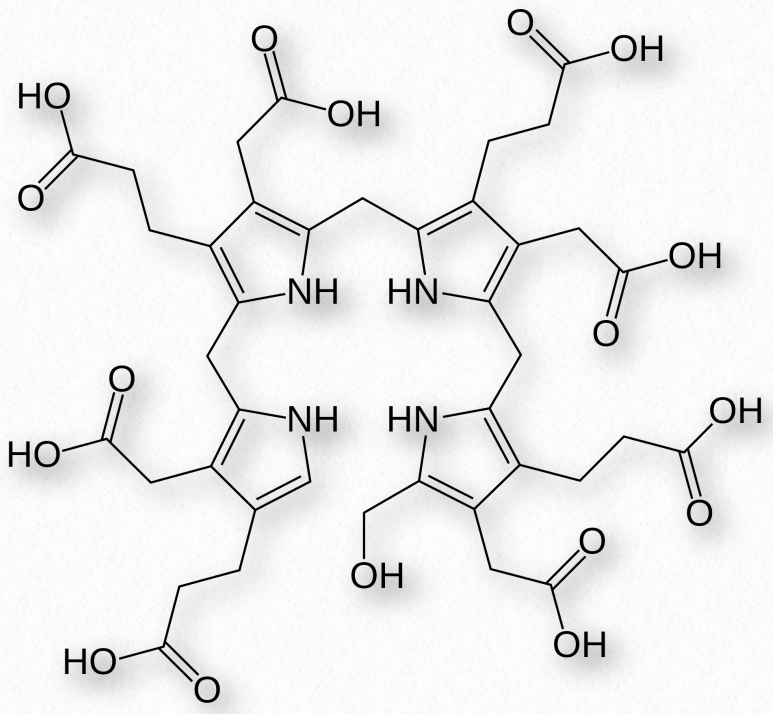


Figure 6.132 - Hydroxylmethylbilane - A precursor of heme

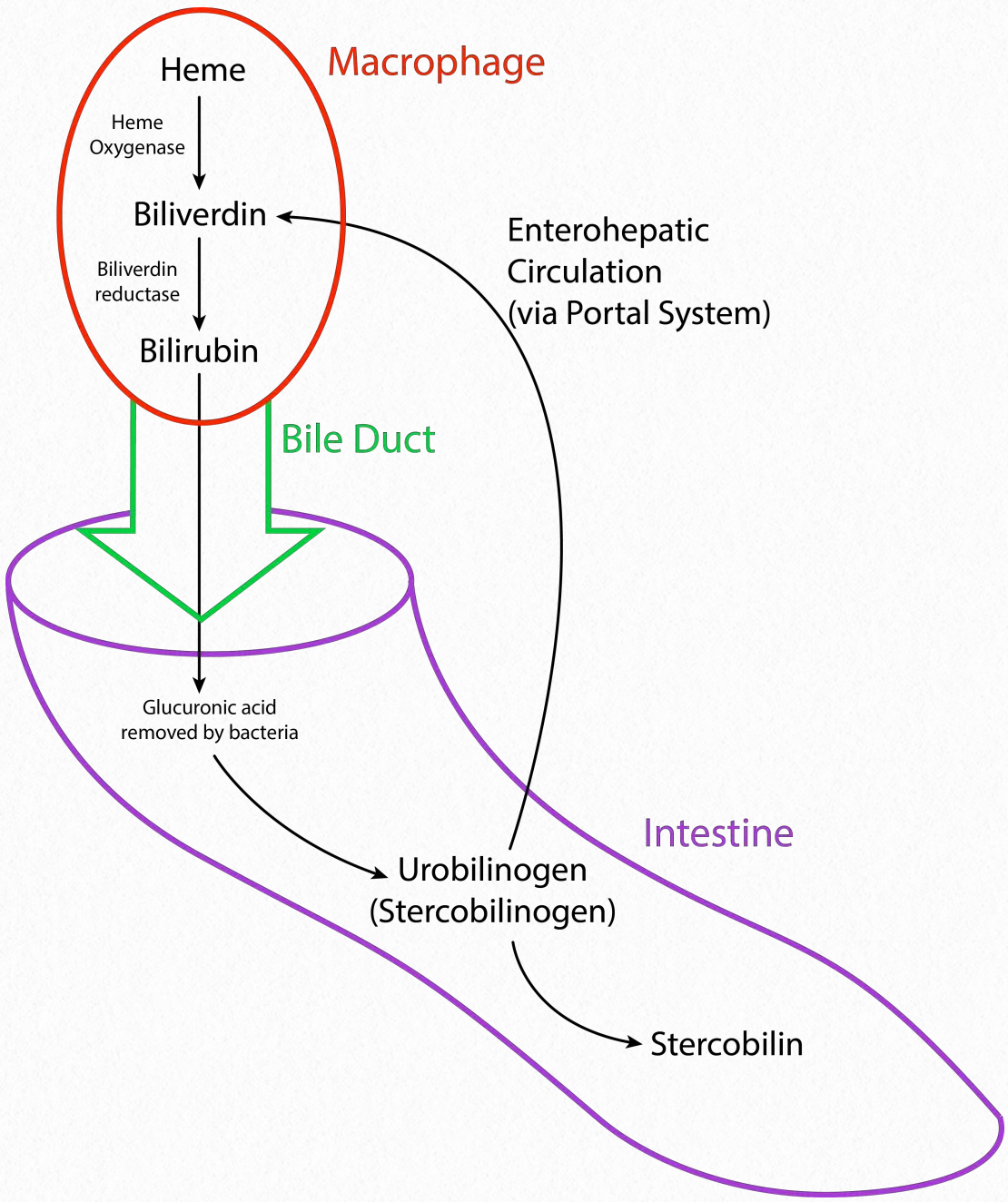


Figure 6.133 - Catabolism of heme

Image by Pehr Jacobson

Severe porphyrias can lead to brain damage, nerve damage, and mental disturbances. The "madness" of King George III may have been due to a form of porphyria. In other manifestations of the disease, cutaneous porphyrias cause skin problems on exposure to light. This need, for patients with certain forms of porphyria, to avoid light, coupled with the fact that porphyrias can be treated by blood tranfusions, may have led to the legend of vampires.

YouTube Lectures by Kevin HERE & HERE

Breakdown of heme

Catabolism of heme (Figure 6.133) begins in macrophages within the spleen . Targets for degradation are hemes within damaged red blood cells, which get removed from the blood supply due to their appearance. It is because of this system, for example, that sickle cell anemia is classified as an anemia (decrease in red blood cells or hemoglobin in the blood). After cells have sickled, they lose their shape and are more likely to be removed from the blood by this process, leaving the patient weakened from low blood cell counts.

The first biochemical step in catabolism is conversion of heme to biliverdin. This reaction is catalyzed by heme oxygenase and requires electrons from NADPH. In the process, Fe^{++} is released. Interestingly, carbon monoxide is also produced and it acts as a vasodilator.

Next, biliverdin is converted to bilirubin by biliverdin reductase and is secreted from the liver into bile. Bacteria in the

intestine convert bilirubin to urobilinogens, some of which is absorbed intestinal cells and transported into kidneys and excreted. The yellow color of urine arises from the compound known as urobilin, which is an oxidation product of urobilinogen. The remainder of the urobilinogens are converted in the intestinal tract to stercobilinogen whose oxidation product is stercobilin and it gives the color associated with feces.

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To Make a Cholesterol

To the tune of "*When Johnny Comes Marching Home*"

Metabolic Melodies Website HERE

Some things that you can build with acetyl-CoAs
Are joined together partly thanks to thiolase
They come together 1-2-3
Six carbons known as H-M-G
And you're on your way
To make a cholesterol

To synthesize a mevalonate in the cell
Requires reducing HMG-CoA, as well
The enzyme is a RE-ductase
Controlled in allosteric ways
When the cell's impelled
To make a cholesterol

The mevalonate made in metabolic schemes
Gets decarboxylated down to isoprenes
They're linked together willy-nil
To build a PP-geranyl
In the cells' routines
To make a cholesterol

A single step links farnesyls but that's not all
The squalene rearranges to lanosterol
From that there's nineteen steps to go
Before the sterol's apropos
Which you must recall
To make a cholesterol

The regulation of the scheme's complex in ways
Inhibited by feedback of the RE-duc-tase
And statins mimic so they say
The look of HMG-CoA
So we sing their praise
And not make cholesterol

Recording by David Simmons
Lyrics by Kevin Ahern

The Dieter's Song

To the tune of "*Story of Love*"

Metabolic Melodies Website HERE

You better lose your middle
Run a little
Get yourself fit as a fiddle
You must break a sweat
You will truly get
Fit

You need to change your diet
Don't deny it
Reducing intake you should try it
Hold off on the cheese
Count the calories,
Love

Bridge
Whenever there is juicy stuff
You need to ponder on the cost
Cuz just a little is enough
Or else your diet's lost

You wanna move your waistline
To the baseline
Give those legs a bit of racetime
It is worth the sweat
When you truly get
Fit

It is worth the sweat
When you truly get
Fit

Recording by David Simmons
Lyrics by Kevin Ahern