Biochemistry

Unit 3 · Lesson 3 · Sphingolipids, steroids and eicosanoids

The notes for Lesson 3 of Unit 3: chapters 3.5 to 3.7 of the unit book, with their figures, worked examples, exam traps and quizzes, in one file. The full unit book, with every chapter, the exam question bank and the glossary, is linked at the end.

Lesson 3 of 3 | 3 chapters | Chapters 3.5 to 3.7

About these notes

These are the notes for **Lesson 3 · Sphingolipids, steroids and eicosanoids** of the University free n easy video lessons on Biochemistry Unit 3, Lipids: Structure and Classification. They are chapters 3.5 to 3.7 of the unit book, unchanged, so a page here is the same page in the full book.

3.5 Sphingolipids and glycolipids

Sphingolipids are membrane lipids built on sphingosine, a long amino alcohol, instead of glycerol. Add one fatty acid to sphingosine and you get ceramide, the parent of the whole family; add phosphocholine to ceramide and you get sphingomyelin, the lipid of the myelin sheath; add sugars and you get the glycosphingolipids: cerebrosides, globosides and gangliosides. Their sugar heads face outwards from the cell and act as labels for recognition, blood groups and toxin binding.

You need: phospholipid structure from 3.4; glycosidic bonds and glycoconjugates from Unit 1.

Sphingosine and ceramide

Sphingosine is an 18-carbon amino alcohol. It has an –OH on C1, an $–NH_2$ on C2, an –OH on C3 and a trans double bond between C4 and C5. Carbons 1 to 3 form a polar region much like the glycerol of a phospholipid, and the long hydrocarbon from C4 onwards acts as the first tail. The cell makes it from palmitoyl-CoA and serine (see Unit 6).

When a fatty acid is joined to the C2 $–NH_2$ by an **amide bond** (not an ester bond), the product is **ceramide**. Ceramide has two tails, like a diacylglycerol, and a free C1 –OH where a head group can attach. Every sphingolipid is ceramide plus a head on C1. Ceramide is also important in its

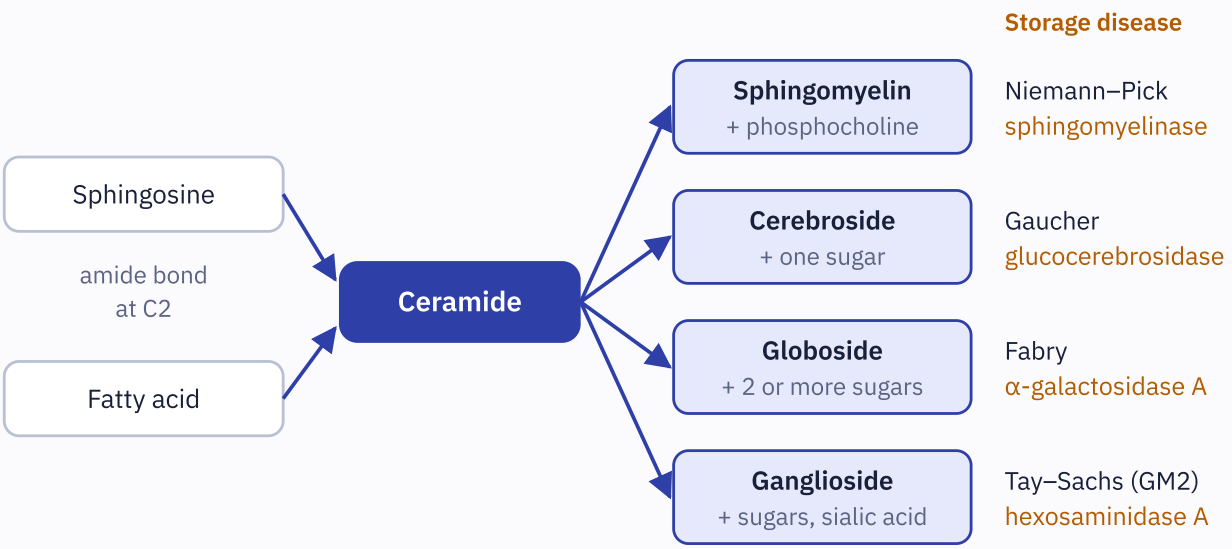
own right: it is a main lipid of the skin barrier in the outer layer of the epidermis, and it acts as a signal for cell stress and apoptosis.

The sphingolipid family

1. **Sphingomyelin** = ceramide + phosphocholine (or phosphoethanolamine) on C1. It contains phosphate, so it is a **phospholipid**, the only sphingolipid that is one in humans. It is rich in the myelin sheath that insulates nerve axons and is found in the outer leaflet of the plasma membrane, where it gathers with cholesterol into ordered patches called lipid rafts.
2. **Cerebrosides** = ceramide + one sugar on C1, through a glycosidic bond, and no phosphate. Galactocerebroside is typical of nerve cell membranes; glucocerebroside occurs in other tissues. A sulfated galactocerebroside is a **sulfatide**.
3. **Globosides** = ceramide + two or more neutral sugars (glucose, galactose, N-acetylgalactosamine). Lactosylceramide is the simplest. Cerebrosides and globosides together are called neutral glycolipids.
4. **Gangliosides** = ceramide + an oligosaccharide carrying one or more **sialic acid** residues (N-acetylneuraminic acid, NeuAc). Sialic acid carries a negative charge, so gangliosides are acidic glycolipids. They are most abundant in the membranes of nerve cells in the grey matter of the brain.

Ganglioside names follow a code: **G** for ganglioside, then **M**, **D** or **T** for one, two or three sialic acids, then a number that rises as the neutral sugar chain gets shorter. So GM1 has the longest sugar chain of the mono-sialo series and GM3 the shortest. GM2 is the one that accumulates in Tay–Sachs disease.

Terpenes are not sphingolipids; they are isoprene-based derived lipids and are taught with the steroids in 3.6.



Each disease: the lysosomal enzyme (orange) is missing, so the lipid in that row piles up.

Figure 3.5.1 Ceramide is the hub. Every sphingolipid is ceramide with a head on C1; the head decides the class. Read each row to the right for the disease caused when the lysosomal enzyme that removes that head (or, for Tay–Sachs, the terminal sugar of GM2) is missing.

Glycolipids and what they do

A **glycolipid** is any lipid with a sugar attached by a glycosidic bond. In animals almost all glycolipids are glycosphingolipids (cerebrosides, globosides, gangliosides). In plants the main ones are **glyceroglycolipids**: monogalactosyl- and digalactosyl-diacylglycerol (MGDG and DGDG) are the most abundant lipids of chloroplast thylakoid membranes.

Glycolipid sugar heads always face the outside of the cell. They work as:

- **Recognition labels.** The ABO blood group antigens are oligosaccharides carried on glycosphingolipids (and glycoproteins) of red cells; group A and B differ by one terminal sugar.
- **Receptors for toxins and microbes.** Cholera toxin binds ganglioside GM1 on intestinal cells before it enters them.
- **Insulation and stability** of myelin (galactocerebroside, sulfatide, sphingomyelin).

Sphingolipid storage diseases

Sphingolipids are broken down step by step in lysosomes, one sugar or head group at a time, each step by its own enzyme. If one enzyme is missing, its substrate cannot be degraded and accumulates in the lysosomes; these are the **sphingolipidoses**, a kind of lysosomal storage disease. Most are autosomal recessive; Fabry disease is X-linked.

DISEASE	ENZYME MISSING	LIPID STORED	MAIN FEATURES
Tay–Sachs	Hexosaminidase A	Ganglioside GM2	neurodegeneration in infancy, cherry-red spot in the retina
Niemann–Pick (A, B)	Sphingomyelinase	Sphingomyelin	enlarged liver and spleen; type A also nerve damage
Gaucher	Glucocerebrosidase (β-glucosidase)	Glucocerebroside	enlarged liver and spleen, bone damage; treated by enzyme replacement
Fabry	α-Galactosidase A	Globotriaosylceramide	pain in hands and feet, kidney and heart damage
Krabbe	Galactocerebrosidase	Galactocerebroside	loss of myelin in infancy

WORKED EXAMPLE

Question (5 marks). A six-month-old child is losing motor skills and the eye doctor sees a cherry-red spot in the macula. A brain biopsy shows lysosomes packed with a ganglioside carrying one sialic acid and three neutral sugars. (a) Name the lipid and the disease. (b) Which enzyme is deficient and which bond does it cut? (c) Why is the brain hit hardest?

1. (a) One sialic acid: the "M" series. The sugar chain is one shorter than GM1's, so it is **GM2**. GM2 storage with a cherry-red spot is **Tay–Sachs disease**.
2. (b) The enzyme is **β-hexosaminidase A**. It removes the terminal N-acetylgalactosamine from GM2, turning it into GM3. Without it, GM2 cannot move down the degradation path.
3. (c) Gangliosides are most concentrated in neurons of the grey matter, so the stored lipid builds up there first and swells and kills nerve cells.

EXAM TRAPS

- The fatty acid in a sphingolipid is joined by an **amide** bond, not an ester bond.
- Sphingomyelin is a phospholipid; cerebrosides and gangliosides are not (no phosphate).
- Glycerol is absent from all sphingolipids. A "sphingolipid with glycerol" is a contradiction.
- Cerebroside = one sugar; ganglioside = sugars plus sialic acid. "Ganglioside without sialic acid" is a globoside.
- Tay–Sachs stores GM2, not GM1. Gaucher stores glucocerebroside, Niemann–Pick stores sphingomyelin; the pairing is asked every year.

CHECK YOURSELF

– REMEMBER **What is ceramide?** 1 mark

Sphingosine with a fatty acid joined by an amide bond to its C2 amino group; the parent of all sphingolipids.

– REMEMBER **Name the enzyme missing in Gaucher disease and the lipid stored.** 2 marks

Glucocerebrosidase (β-glucosidase); glucocerebroside accumulates.

– UNDERSTAND **Why are gangliosides negatively charged at pH 7?** 2 marks

They contain sialic acid (N-acetylneuraminic acid), whose carboxyl group is ionised to $-COO^-$ at pH 7.

– UNDERSTAND **How do glycolipids help a cell to be recognised?** 3 marks

Their oligosaccharide heads stick out from the outer leaflet, and the exact sugar sequence differs between cell types and individuals. Antibodies, lectins, toxins and other cells bind specific sequences, as with ABO blood group antigens and cholera toxin binding GM1.

– APPLY **Hydrolysis of a lipid gives sphingosine, a fatty acid and galactose only. Name and classify it.** 2 marks

Galactocerebroside: a neutral glycosphingolipid (cerebroside), a compound lipid with no phosphate.

– APPLY **Give one difference and one similarity between sphingomyelin and lecithin.** 2 marks

Difference: sphingomyelin has sphingosine and an amide-linked fatty acid; lecithin has glycerol and two ester-linked fatty acids. Similarity: both carry phosphocholine as head group and both are amphipathic membrane phospholipids.

– ANALYZE **Gaucher disease can be treated by giving the enzyme intravenously, but Tay–Sachs cannot be treated this way. Suggest why.** 4 marks

Gaucher mainly affects macrophages of liver, spleen and bone marrow, which take up infused enzyme from blood. Tay–Sachs damage is in neurons of the brain, and the large enzyme protein cannot cross the blood–brain barrier, so infused enzyme does not reach the stored GM2.

BEYOND THE SYLLABUS

Substrate reduction therapy treats some sphingolipidoses by blocking the enzyme that makes glucosylceramide, so less lipid needs breaking down. Gene therapy and brain-penetrating enzymes are being tested for the neurological forms. Sphingosine-1-phosphate is a signalling lipid, and fingolimod, a drug for multiple sclerosis, acts on its receptors. This is not for the exam; search "substrate reduction therapy Gaucher" and "sphingosine-1-phosphate signalling" to go further.

3.6 Cholesterol and steroids

Steroids are lipids built on a rigid frame of four fused rings, the steroid nucleus. Cholesterol is the main steroid of animal cells: it stiffens and seals membranes, and it is the raw material for bile acids, the steroid hormones and vitamin D. It has no fatty acid and no ester bond in its free form, which is why it is classed as a derived lipid. Because it is insoluble in blood, it travels inside lipoproteins, and the balance between LDL and HDL cholesterol is one of the strongest predictors of heart disease.

You need: classification of derived lipids from 3.1; amphipathic membrane lipids from 3.4.

The steroid nucleus and cholesterol

The steroid nucleus is **cyclopentanoperhydrophenanthrene**: three six-membered rings (A, B, C) fused like phenanthrene, fully saturated ("perhydro"), with a five-membered ring D attached. It has 17 carbons, numbered in a fixed order that every steroid uses. Any molecule with this nucleus is a steroid; a steroid with an –OH at C3 is a **sterol**.

Cholesterol ($C_{27}H_{46}O$) adds four features to the nucleus (Figure 3.6.1):

- a **3β-hydroxyl** group on ring A, its only polar group;
- a **double bond between C5 and C6** in ring B;
- two **methyl groups**, C19 on C10 and C18 on C13;
- an **eight-carbon branched side chain** on C17 (carbons 20 to 27).

The –OH is a tiny head on a large flat hydrophobic body, so cholesterol is only weakly amphipathic. In membranes it sits between phospholipids with its –OH near their head groups. When the –OH is esterified with a fatty acid, the product, **cholesteryl ester**, is even more hydrophobic; this is the form stored in cells and carried in the core of lipoproteins.

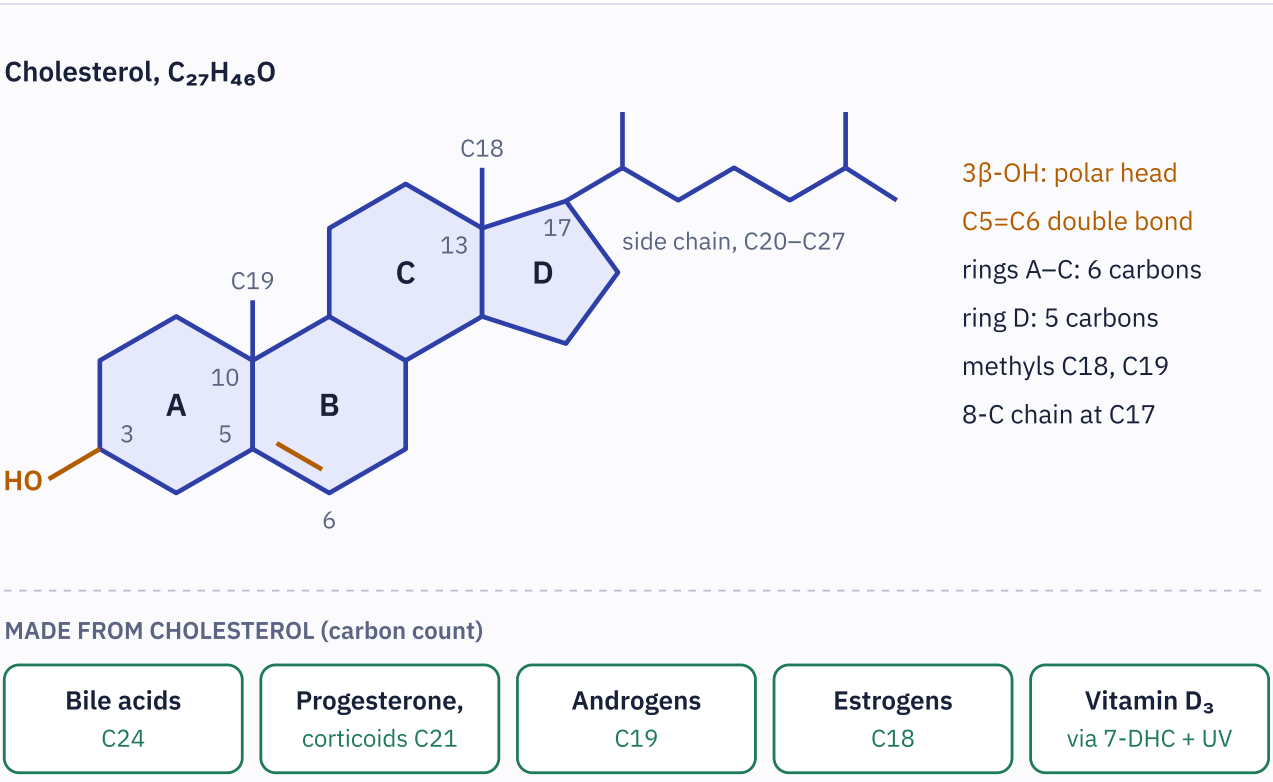


Figure 3.6.1 The steroid nucleus as it appears in cholesterol. Rings A, B and C have six carbons, ring D five. Orange marks the two features examiners ask about most, the 3β-OH and the C5=C6 double bond. The bottom row shows the steroid families the body makes from cholesterol, each with its carbon count, which falls as the side chain is cut away.

What cholesterol does

1. **Membrane fluidity buffer.** Its rigid rings restrict the movement of nearby fatty acid chains, so membranes are less fluid at body temperature; it also keeps chains from packing into a solid gel when cold. Animal plasma membranes contain a large share of cholesterol; plants use phytosterols such as β-sitosterol and stigmasterol, and fungi use **ergosterol**, which is the target of antifungal drugs such as amphotericin B and the azoles. Most bacteria have no sterols.

2. **Bile acids.** The liver converts cholesterol to the C24 **primary bile acids**, cholic acid and chenodeoxycholic acid; the first step is 7α-hydroxylation. They are joined (conjugated) to glycine or taurine, giving **bile salts** such as glycocholate and taurocholate. Bile salts are strong amphipathic detergents that emulsify dietary fat and form micelles for its absorption. Gut bacteria convert some to **secondary bile acids** (deoxycholic and lithocholic acid). About 95 percent of bile salts are reabsorbed and returned to the liver (enterohepatic circulation); the rest is lost in faeces, and this is the body's main way of getting rid of cholesterol.

3. **Steroid hormones.** In mitochondria of the adrenal cortex and gonads, the side chain is cut to give **pregnenolone** (C21), the common parent. From it come progesterone (C21), the

glucocorticoids (cortisol, C21), the **mineralocorticoids** (aldosterone, C21), the androgens (testosterone, C19) and the estrogens (estradiol, C18, with an aromatic ring A).

4. **Vitamin D.** In the skin, ultraviolet B light opens ring B of 7-dehydrocholesterol, an intermediate of cholesterol synthesis, giving vitamin D_3 (cholecalciferol). Its activation and functions are in Unit 4.

Cortisol is made in the zona fasciculata of the adrenal cortex; it raises blood glucose by promoting gluconeogenesis, breaks down muscle protein and suppresses inflammation and immunity, which is why synthetic glucocorticoids (prednisolone, dexamethasone) are used against inflammation. **Aldosterone** is made in the zona glomerulosa; it acts on the kidney to retain Na^+ (and with it water) and excrete K^+, so it controls blood volume and pressure.

Terpenes: the isoprene family

Terpenes (isoprenoids) are derived lipids built from five-carbon **isoprene** units (2-methyl-1,3-butadiene). They are classed by how many units they contain:

CLASS	ISOPRENE UNITS	CARBONS	EXAMPLES
Monoterpenes	2	C10	menthol, limonene, geraniol
Sesquiterpenes	3	C15	farnesol
Diterpenes	4	C20	phytol (side chain of chlorophyll), retinol, gibberellins
Triterpenes	6	C30	squalene, the precursor of cholesterol
Tetraterpenes	8	C40	carotenoids: β-carotene, lycopene
Polyterpenes	many	—	natural rubber

Steroids are modified triterpenes: the cell builds squalene from six isoprene units and folds it into the four rings, losing three carbons on the way to cholesterol (C27). The pathway from acetyl-CoA through HMG-CoA and the action of statins are in Unit 6, Synthesis of triacylglycerols, phospholipids and cholesterol.

Lipoproteins and heart disease

A **lipoprotein** is a particle with a core of TAG and cholesteryl ester and a shell of phospholipid, free cholesterol and proteins called apolipoproteins. The classes, from largest and least dense to smallest and densest, are:

- **Chylomicrons**: carry dietary TAG from the intestine.
- **VLDL**: carry TAG made in the liver to tissues; as they lose TAG they become IDL and then LDL.

- **LDL**: carry most of the blood's cholesterol to tissues, taken up through the LDL receptor. Called "bad cholesterol" because excess LDL enters artery walls, is oxidised and taken up by macrophages, which become foam cells and build **atherosclerotic plaque**.
- **HDL**: collect excess cholesterol from tissues and return it to the liver (reverse cholesterol transport), helped by LCAT. Called "good cholesterol" because higher HDL goes with lower risk.

Commonly used adult targets (US NCEP ATP III, also used in Indian labs) are total cholesterol below 200 mg/dL, LDL below 100 mg/dL as optimal, HDL of 60 mg/dL or more as protective (below 40 is low), and fasting TAG below 150 mg/dL. In familial hypercholesterolaemia, a faulty LDL receptor keeps LDL high from birth and causes early heart attacks.

Two colour tests detect cholesterol in the lab. In the **Liebermann–Burchard test**, cholesterol in chloroform with acetic anhydride and concentrated sulfuric acid turns green. In the **Salkowski test**, chloroform and concentrated sulfuric acid give a red colour in the chloroform layer.

WORKED EXAMPLE

Question (5 marks). A 45-year-old's fasting lipid profile reads: total cholesterol 230 mg/dL, HDL 38 mg/dL, triacylglycerol 160 mg/dL. (a) Estimate LDL cholesterol with the Friedewald formula. (b) Find the total cholesterol/HDL ratio. (c) Comment on the risk.

1. Friedewald formula (all values in mg/dL, valid when TAG is below 400 mg/dL): LDL = TC − HDL − TAG/5. Here TAG/5 = 160/5 = 32 mg/dL estimates VLDL cholesterol.
2. LDL = 230 − 38 − 32 = **160 mg/dL**.
3. TC/HDL = 230 / 38 = **6.1**.
4. Comment: total cholesterol is above 200, LDL is well above the optimal 100, HDL is below 40 and TAG is just above 150. With a high TC/HDL ratio as well, this person has raised cardiovascular risk and needs diet, exercise and possibly a statin, as a doctor decides.

EXAM TRAPS

- Cholesterol is a derived lipid (steroid alcohol), not a fat. It gives no energy; the body cannot break the ring system down to CO_2.
- The double bond is between C5 and C6, in ring B, not in ring A.
- "Good" and "bad" cholesterol are the same molecule; the labels describe the carrier, HDL or LDL.
- Bile acids are C24 and come from cholesterol; bile pigments (bilirubin) come from haem. Do not mix them up.
- Steroids are made from squalene, a triterpene; carotenoids are tetraterpenes. Count isoprene units carefully.

CHECK YOURSELF

– REMEMBER **What is the parent ring system of all steroids called?** 1 mark

Cyclopentanoperhydrophenanthrene (the steroid nucleus): three six-membered rings and one five-membered ring.

– REMEMBER **Name two primary bile acids and the amino acids they are conjugated with.** 2 marks

Cholic acid and chenodeoxycholic acid; conjugated with glycine or taurine.

– UNDERSTAND **How does cholesterol keep membrane fluidity steady?** 3 marks

Its rigid rings reduce the motion of nearby fatty acid chains, lowering fluidity at high temperature; at low temperature it gets between chains and stops them packing into a gel. So it buffers fluidity against temperature change.

– UNDERSTAND **Why is LDL called "bad" and HDL "good" cholesterol?** 3 marks

LDL delivers cholesterol to tissues; excess LDL enters artery walls, is oxidised and forms foam cells and plaque. HDL removes cholesterol from tissues back to the liver. High LDL raises, and high HDL lowers, the risk of atherosclerosis.

– APPLY **Total cholesterol 190 mg/dL, HDL 50 mg/dL, TAG 100 mg/dL. Estimate LDL.** 2 marks

LDL = 190 − 50 − 100/5 = 190 − 50 − 20 = **120 mg/dL** (near optimal, above 100).

– APPLY **Classify by isoprene units: β-carotene, menthol, squalene.** 3 marks

β-Carotene: tetraterpene (8 units, C40). Menthol: monoterpene (2 units, C10). Squalene: triterpene (6 units, C30).

– ANALYZE **Bile acid sequestrant drugs bind bile salts in the gut and stop their reabsorption. Why does this lower blood cholesterol?** 4 marks

Bile salts lost in faeces are not returned to the liver, so the liver must make new bile acids from cholesterol. It takes more LDL from blood (more LDL receptors) to supply this, and blood LDL cholesterol falls. It uses the main excretion route of cholesterol on purpose.

BEYOND THE SYLLABUS

Newer cholesterol-lowering drugs block PCSK9, a protein that destroys LDL receptors, using monoclonal antibodies or small interfering RNA. Lipoprotein(a), a modified LDL particle, is now measured as an inherited risk factor. Bacteria use hopanoids, sterol-like molecules, to stiffen their membranes, and their fossils are used as molecular markers of ancient life. This is not for the exam; search "PCSK9 inhibitors" and "lipoprotein(a) risk" to go further.

3.7 Eicosanoids

Eicosanoids are signalling molecules made from 20-carbon polyunsaturated fatty acids, mainly arachidonic acid ("eicosa" is Greek for twenty). They include the prostaglandins, prostacyclin, the thromboxanes and the leukotrienes. Unlike classical hormones they are not stored and do not travel far: a cell makes them within seconds when stimulated, they act on the same cell or its neighbours, and they are destroyed quickly. They control pain, fever, inflammation, blood clotting, labour and airway tone, which makes them the targets of some of the most used drugs in the world, from aspirin to asthma tablets.

You need: arachidonic acid and ω-numbering from 3.2; phospholipase A2 from 3.4.

Precursors and the three families

Arachidonic acid, 20:4(Δ5,8,11,14), is an ω-6 fatty acid stored at sn-2 of membrane phospholipids. When a cell receives a signal (injury, a hormone, an immune trigger), **phospholipase A2** cuts it free. This release is the controlling step: no free arachidonic acid, no eicosanoids. Then two main enzyme routes act on it:

1. **Cyclooxygenase (COX) pathway**, the "cyclic" route. The enzyme, also called prostaglandin H synthase, adds two O_2 and closes a ring, giving PGG_2 and then **PGH_2**. Tissue-specific

enzymes turn PGH_2 into the **prostanoids**: prostaglandins (PGE_2, $PGF_2\alpha$, PGD_2), **prostacyclin** (PGI_2, mainly in vessel walls) and **thromboxane A_2** (TXA_2, mainly in platelets). There are two forms of the enzyme: **COX-1**, made all the time in most tissues (stomach, platelets, kidney), and **COX-2**, switched on at sites of inflammation.

2. **Lipoxygenase (LOX) pathway**, the "linear" route. **5-Lipoxygenase**, mainly in white blood cells, gives LTA_4 and then the **leukotrienes** LTB_4, LTC_4, LTD_4 and LTE_4. Other lipoxygenases give lipoxins and hydroxy acids.
3. A third, smaller route uses **cytochrome P450** enzymes to make epoxy acids that act on blood vessels.

The precursor sets the "series". Arachidonic acid gives series-2 prostanoids (two double bonds, the subscript in PGE_2) and series-4 leukotrienes. The ω-3 fatty acid EPA, 20:5, gives series-3 prostanoids and series-5 leukotrienes, which are generally weaker promoters of inflammation and clotting. This is one reason fish oil is studied for heart health.

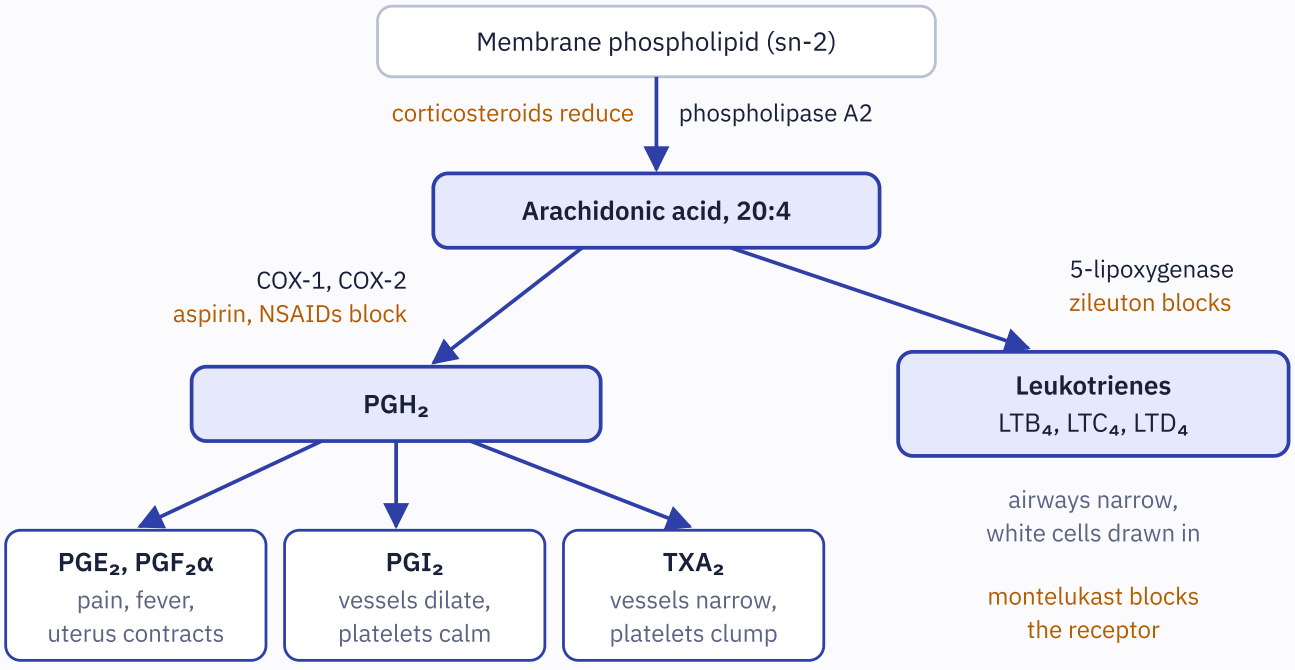


Figure 3.7.1 One fatty acid, two routes. Phospholipase A2 releases arachidonic acid; cyclooxygenase sends it to PGH_2 and the prostanoids (left), 5-lipoxygenase to the leukotrienes (right). Orange shows where common drugs act. Notice that PGI_2 and TXA_2 come from the same PGH_2 yet have opposite effects on vessels and platelets.

Structures and actions

Prostaglandins are built on prostanoic acid, a C20 acid with a five-membered (cyclopentane) ring formed between C8 and C12. The letter after PG (A to I) tells the groups on the ring; the

subscript tells the number of C=C double bonds in the side chains. They were named in the 1930s by Ulf von Euler, who found them in seminal fluid and believed they came from the prostate gland. Sune Bergström, Bengt Samuelsson and John Vane shared the 1982 Nobel Prize in Physiology or Medicine for this field.

Thromboxanes have a six-membered ring that contains an oxygen atom. **Leukotrienes** have no ring; they have three conjugated double bonds (a "triene") and were first found in leukocytes, hence the name. LTC_4, LTD_4 and LTE_4 carry cysteine-containing groups and together were once called the slow-reacting substance of anaphylaxis.

The actions to remember:

- **PGE_2**: causes fever (acts on the hypothalamus), pain and the redness and swelling of inflammation; protects the stomach lining by reducing acid and increasing mucus; keeps the ductus arteriosus open before birth.
- **$PGF_2\alpha$**: contracts the uterus (labour, menstrual cramps) and constricts bronchi.
- **PGI_2 (prostacyclin)**: made by the endothelium; dilates vessels and prevents platelets from clumping.
- **TXA_2**: made by platelets; constricts vessels and makes platelets clump, starting a clot.
- **Leukotrienes**: LTB_4 attracts neutrophils; LTC_4 and LTD_4 constrict airways strongly and make vessels leaky, as in asthma and allergy.

Eicosanoids act through cell-surface G-protein-coupled receptors, which change cAMP or Ca^{2+} inside the cell.

Drugs that act on the pathway

1. **Aspirin** transfers an acetyl group to a serine in the active site of COX, blocking it permanently. **Ibuprofen** and other NSAIDs block it reversibly. Both reduce PGE_2, so they lower fever, pain and inflammation, but by also blocking COX-1 in the stomach they reduce its protection and can cause ulcers.
2. **COX-2 selective inhibitors** (coxibs such as celecoxib) were made to spare the stomach. Some raised the risk of heart attacks, and rofecoxib was withdrawn in 2004, because blocking endothelial PGI_2 while platelet TXA_2 continues tips the balance toward clotting.
3. **Corticosteroids** reduce PLA2 activity and the production of COX-2, so they cut both branches; this is part of their strong anti-inflammatory effect.
4. **Leukotrienes** are targeted in asthma: montelukast blocks their receptor and zileuton inhibits 5-lipoxygenase.
5. Prostaglandin analogues are used as drugs: misoprostol (a PGE_1 analogue) protects the stomach and is used in obstetrics; latanoprost (a $PGF_2\alpha$ analogue) treats glaucoma.

WORKED EXAMPLE

Question (6 marks). A doctor prescribes 75 mg of aspirin daily to a patient after a heart attack. Explain, using the eicosanoid pathway, how such a low dose prevents clots in arteries without stopping prostacyclin production for long.

1. Clotting in arteries starts when platelets clump, driven by TXA_2 made in platelets by COX-1. Prostacyclin (PGI_2) from the endothelium opposes this.
2. Aspirin acetylates COX **irreversibly**. A blocked enzyme stays blocked until the cell makes new enzyme.
3. Platelets have **no nucleus**, so they cannot make new COX. Each exposed platelet stays unable to make TXA_2 for its whole life of about 7 to 10 days.
4. Endothelial cells have a nucleus and make fresh COX within hours, so PGI_2 production recovers between doses.
5. Result: a daily low dose keeps TXA_2 low and lets PGI_2 recover, shifting the balance away from clotting. A higher dose would block more endothelial COX and stomach COX-1 with no extra benefit and more side effects.

EXAM TRAPS

- Aspirin blocks cyclooxygenase, not lipoxygenase. It does not lower leukotrienes, and in some people it can even worsen asthma.
- Prostacyclin (PGI_2) and thromboxane (TXA_2) have opposite effects; do not list both as "pro-clotting".
- The subscript in PGE_2 is the number of double bonds in the side chains, not a type number. Series 2 comes from arachidonic acid.
- Eicosanoids are local (autocrine and paracrine) mediators made on demand, not stored hormones carried in blood.
- Favourite question: "Write the biosynthesis and functions of prostaglandins" or "Explain the action of aspirin".

CHECK YOURSELF

– REMEMBER **Name the precursor of series-2 prostaglandins and the enzyme that releases it.** 2 marks

Arachidonic acid, 20:4(Δ5,8,11,14); released from membrane phospholipids by phospholipase A2.

– REMEMBER **List the main classes of eicosanoids.** 2 marks

Prostaglandins, prostacyclin, thromboxanes (together the prostanoids) and leukotrienes; also lipoxins.

– UNDERSTAND **Why are eicosanoids called local hormones?** 2 marks

They are made on demand by many cell types and act on the same or neighbouring cells within seconds to minutes before being inactivated, instead of travelling in blood from one gland to distant targets.

– UNDERSTAND **Why can long-term NSAID use cause stomach ulcers?** 3 marks

COX-1 in the stomach makes PGE_2 and PGI_2, which reduce acid secretion and increase mucus and blood flow. NSAIDs block COX-1, so this protection is lost and acid damages the lining.

– APPLY **A diet rich in fish oil raises EPA in membranes. Which prostanoid and leukotriene series would increase?** 2 marks

EPA (20:5) gives series-3 prostanoids (such as TXA_3, PGI_3) and series-5 leukotrienes (such as LTB_5).

– APPLY **Choose a drug to block (a) fever, (b) asthma attacks driven by leukotrienes, (c) all branches of the pathway.** 3 marks

(a) Aspirin, ibuprofen or another NSAID (COX inhibition). (b) Montelukast (receptor blocker) or zileuton (5-LOX inhibitor). (c) A corticosteroid, which reduces PLA2 activity and COX-2 production.

– ANALYZE **Explain how selective COX-2 inhibitors can protect the stomach yet raise the risk of heart attack.** 4 marks

They spare COX-1, so gastric prostaglandins and platelet TXA_2 continue. They block COX-2, which contributes much of the endothelial PGI_2. With PGI_2 lowered and TXA_2 unchanged, the balance shifts toward vasoconstriction and platelet clumping, increasing clot risk in coronary arteries.

BEYOND THE SYLLABUS

Inflammation does not just fade; it is actively switched off by specialised pro-resolving mediators such as lipoxins, resolvins and protectins, many made from ω-3 fatty acids. Drug research is moving from blocking eicosanoids to boosting this resolution phase. Lipidomic mass spectrometry now measures dozens of eicosanoids in a drop of blood. This is not for the exam; search "resolvins inflammation resolution" and "eicosanoid lipidomics" to go further.

Key terms of this lesson

TERM	MEANING OR FORMULA	CHAPTER
Ceramide	sphingosine + amide-linked fatty acid; parent of sphingolipids	3.5
Ganglioside	ceramide + oligosaccharide with sialic acid; GM2 stored in Tay–Sachs	3.5
Cholesterol	$C_{27}H_{46}O$; steroid nucleus, 3β-OH, C5=C6, side chain at C17	3.6
Friedewald formula	LDL = TC − HDL − TAG/5 (mg/dL, TAG below 400)	3.6
Isoprene unit	C5 building block of terpenes; squalene (C30) → steroids	3.6
COX / 5-LOX	arachidonic acid → PGH_2 → prostanoids / → leukotrienes	3.7

Glossary (terms used in this lesson)

Amphipathic Having a polar and a non-polar part in one molecule.

Arachidonic acid 20:4(Δ5,8,11,14), ω-6; precursor of series-2 prostanoids.

Bile salt Bile acid conjugated to glycine or taurine; emulsifies fat.

Ceramide Sphingosine with an amide-linked fatty acid; parent of sphingolipids.

Cerebroside Ceramide with one sugar (glucose or galactose).

Cholesteryl ester Cholesterol esterified at its 3-OH with a fatty acid.

Cyclooxygenase (COX) Enzyme converting arachidonic acid to PGH_2; target of aspirin.

Eicosanoid Signalling molecule made from a C20 polyunsaturated fatty acid.

Ganglioside Ceramide with an oligosaccharide containing sialic acid.

Isoprene	Five-carbon unit from which terpenes and steroids are built.
Lecithin	Phosphatidylcholine.
Leukotriene	Linear eicosanoid from 5-lipoxygenase; constricts airways.
Lipoprotein	Particle of lipid and apolipoprotein that carries lipids in blood.
Prostacyclin	PGI_2; vasodilator that prevents platelet clumping.
Sphingosine	C18 amino alcohol backbone of sphingolipids.
Steroid nucleus	Cyclopentanoperhydrophenanthrene: four fused rings A–D.
Thromboxane A_2	Platelet eicosanoid that constricts vessels and aggregates platelets.
Triacylglycerol	Glycerol esterified with three fatty acids; storage fat.

The full unit book

Every chapter of Unit 3, the unit summary, the exam question bank with model answers and the full glossary: Biochemistry · Unit 3 · Lipids: Structure and Classification (one file, works offline).

Sources and further reading

Textbooks

- D. L. Nelson and M. M. Cox, *Lehninger Principles of Biochemistry*, W. H. Freeman; the chapter on lipids and the chapter on lipid biosynthesis (from memory; check).
- J. M. Berg, J. L. Tymoczko, G. J. Gatto and L. Stryer, *Biochemistry*, W. H. Freeman; chapters on membrane lipids and lipid metabolism (from memory; check).
- D. Voet and J. G. Voet, *Biochemistry*, Wiley (from memory; check).
- U. Satyanarayana and U. Chakrapani, *Biochemistry*, a widely used Indian textbook; the chapter on lipids (from memory; check).
- V. W. Rodwell and others, *Harper's Illustrated Biochemistry*, McGraw-Hill, for lipoproteins and clinical aspects (from memory; check).

Open web resources

- LIPID MAPS, Lipid Classification System: lipidmaps.org/resources/education/classification (the eight lipid categories).
- FSSAI, news compilation on the trans fat regulation of December 2020: fssai.gov.in (PDF) (limit of 2 percent in oils and fats from January 2022).

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