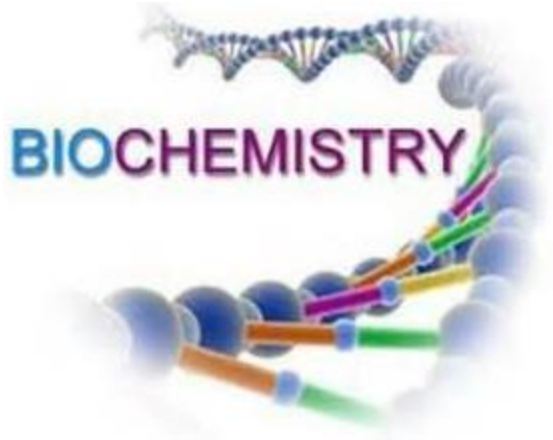
CHAPTER 10

Lipids

Xianming Deng



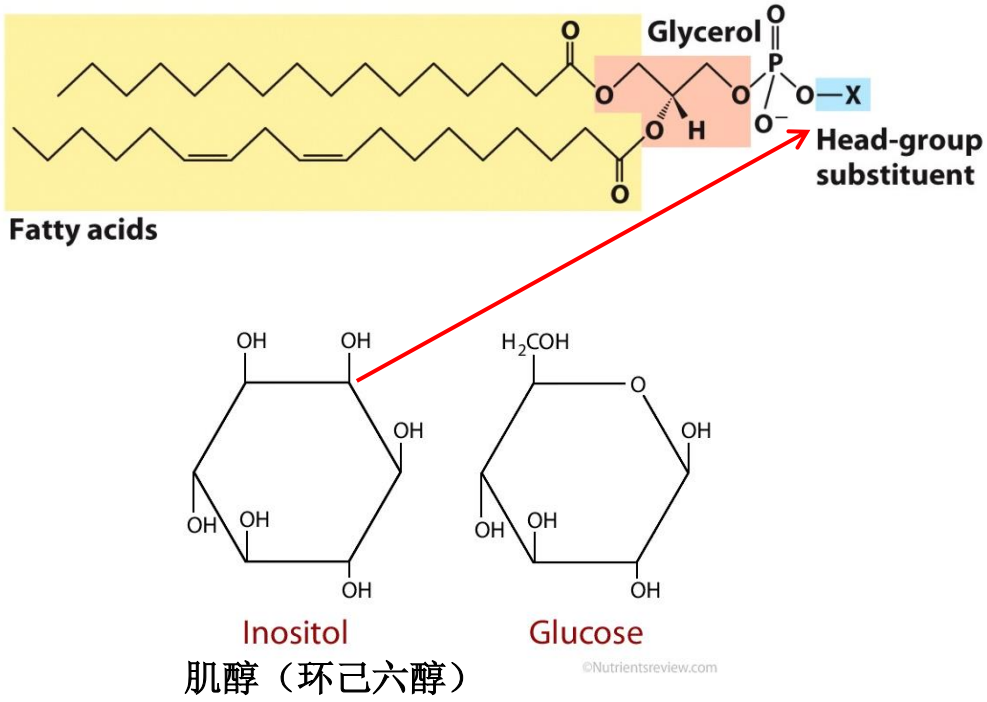
10.3 Lipids as Signals, Cofactors, and Pigments

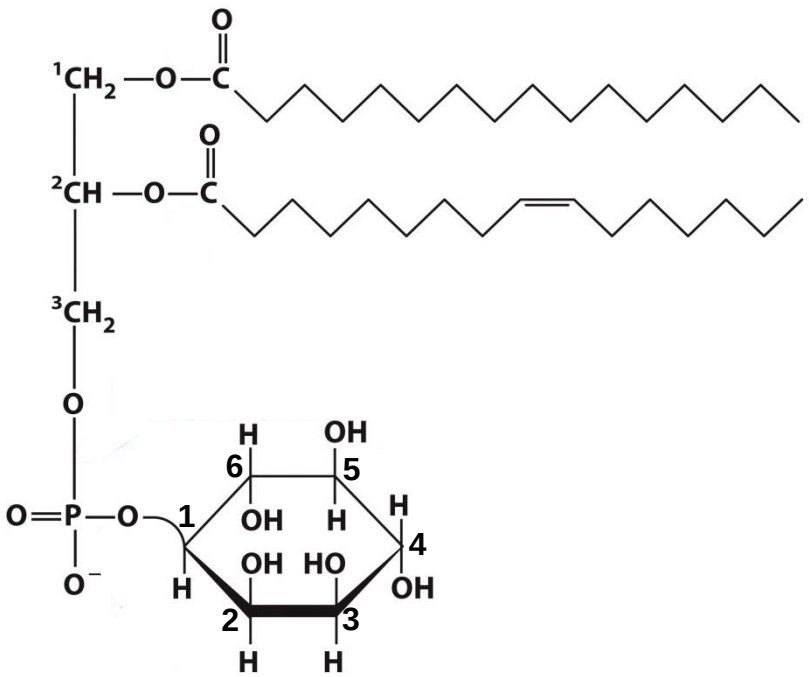
➢ *Passive* and *active* roles of lipids in cells

- **Storage lipids** and **structural lipids** are major cellular components that play a ***passive*** role in the cell.
  - **Membrane lipids** make up 5% to 10% of the dry mass of most cells.
  - **Storage lipids** make up more than 80% of the mass of an adipocyte.
- Another group of lipids, present in much smaller amounts, have ***active*** roles in the metabolic traffic as metabolites and messengers.
  - **Potent signals**: as hormones, or as intracellular messengers
  - **Enzyme cofactors**: in electron-transfer reactions, or in the transfer of sugar moieties
  - **Pigment molecules**: Vitamin A, D, E, K

■ Phosphatidylinositols（磷脂酰肌醇)

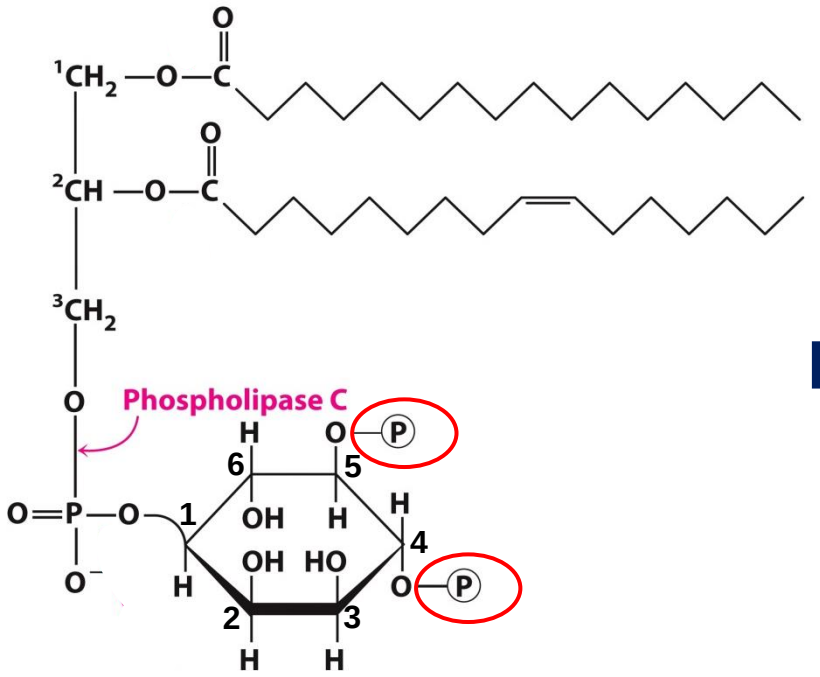
- **Inositol and phosphatidylinositol**



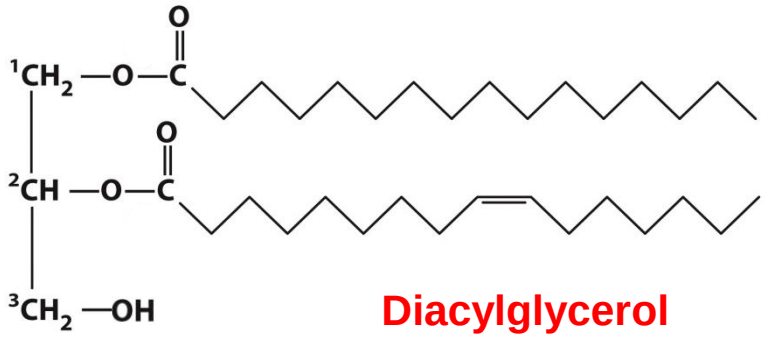


Phosphatidylinositol

- **Hydrolysis of phosphatidylinositol 4,5-bisphosphate releases inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol**

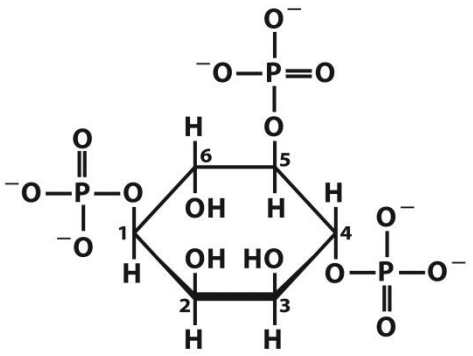


Phosphatidylinositol 4,5-bisphosphate (PIP_2)



Diacylglycerol

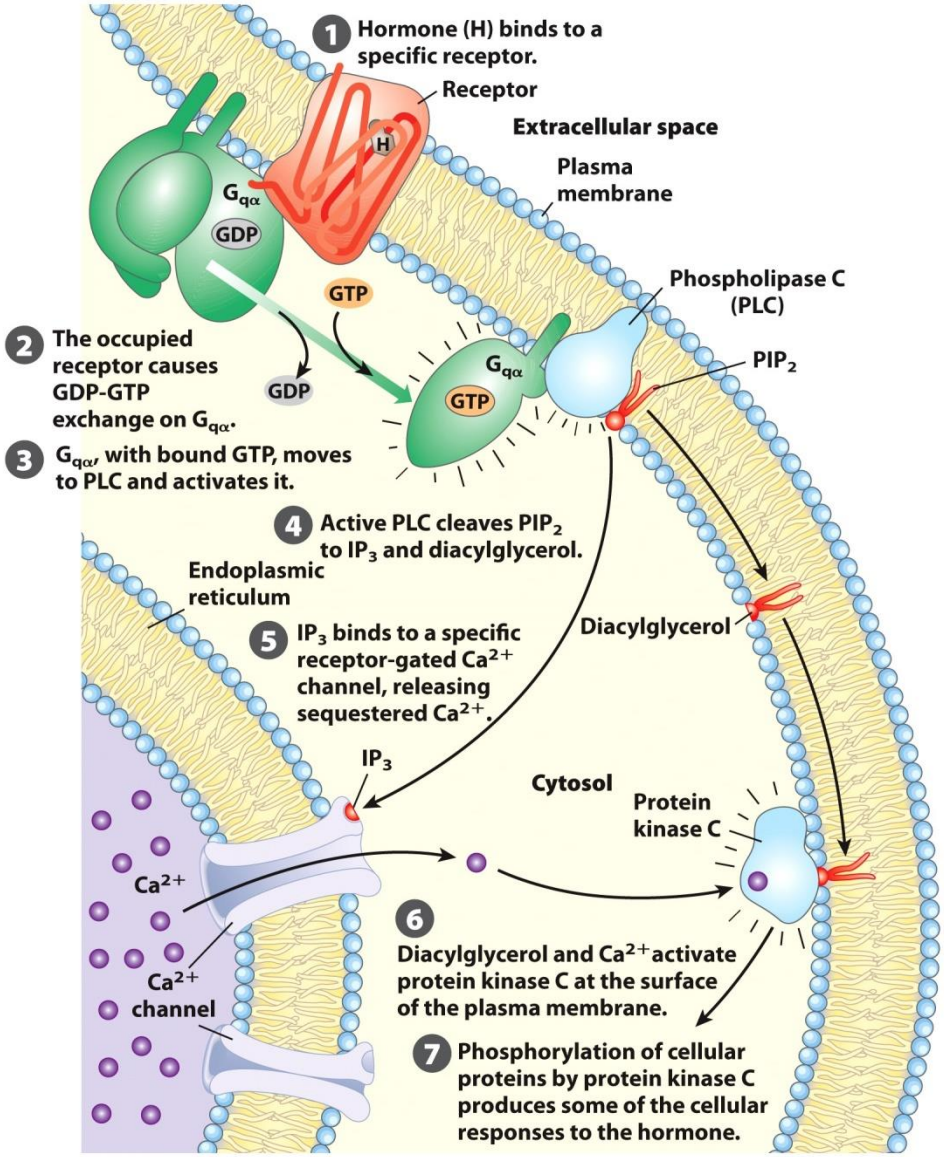
+



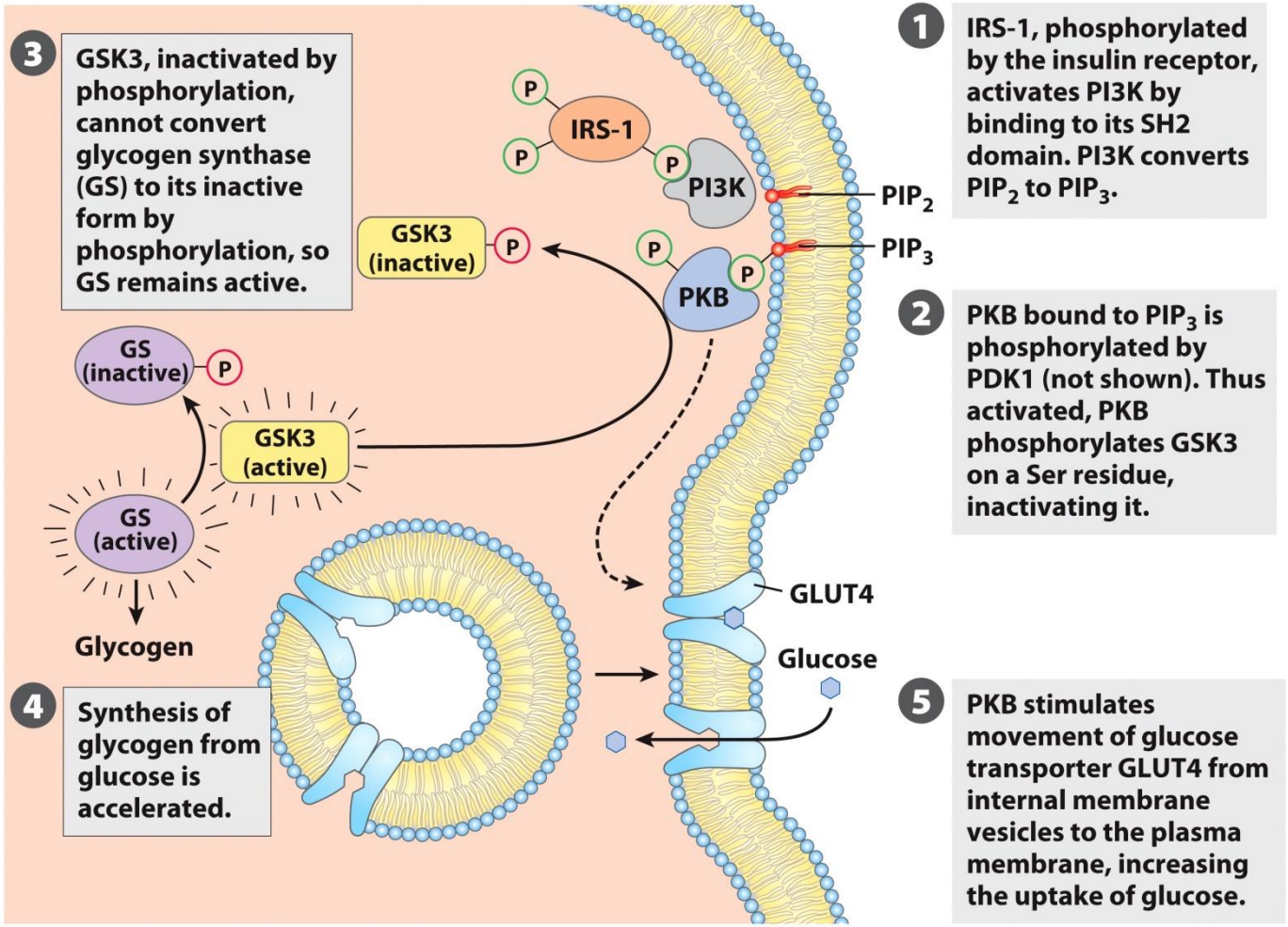
Inositol 1,4,5-trisphosphate (IP_3)

- **Phosphatidylinositol and its phosphorylated derivatives act at intracellular signals**

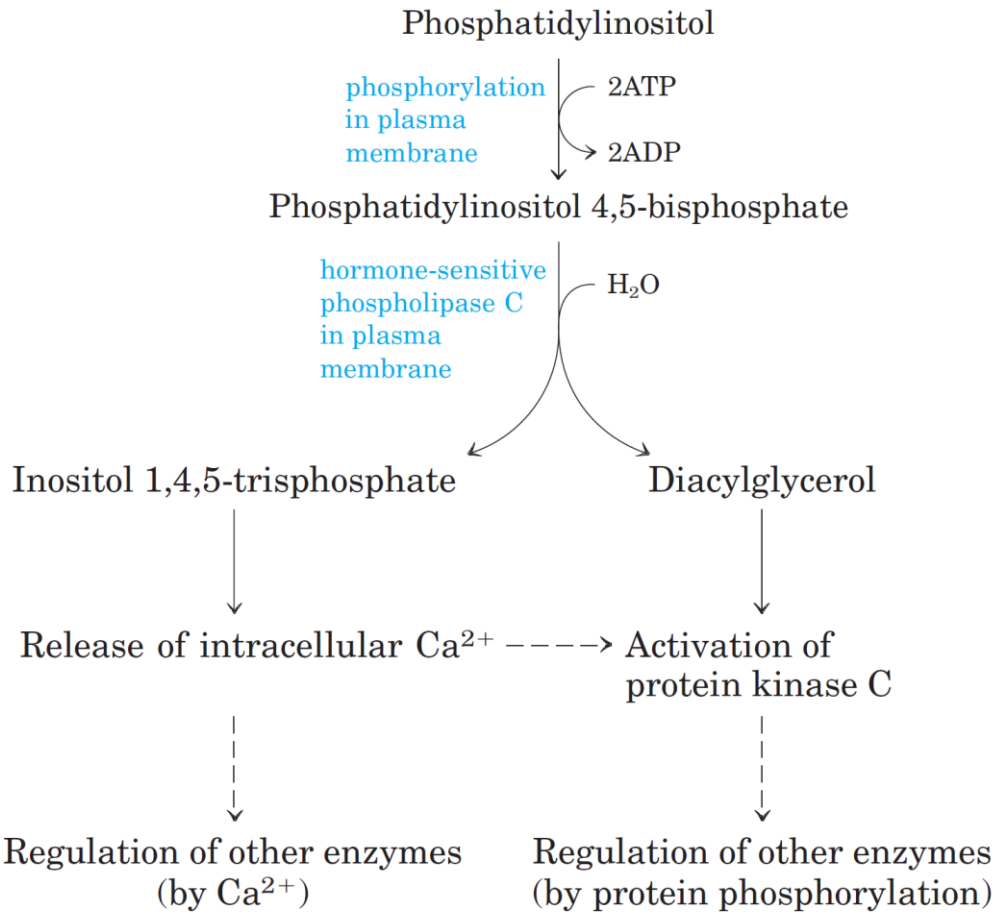
Phosphatidylinositol 4,5-bisphosphate in the cytoplasmic (inner) face of plasma membranes serves as a reservoir of messenger molecules that are released inside the cell in response to extracellular signals interacting with specific surface receptors.



- **Signaling regulated by phosphatidylinositol 4,5-trisphosphate (PIP_2) and phosphatidylinositol 3,4,5-trisphosphate (PIP_3)**



Phosphatidylinositols in cellular regulation.



Discovery of PI3K kinase

Lewis C. Cantley

Director (2012-)

Cancer Center of Weill Cornell Medical College and NewYork-Presbyterian Hospital

In 1985 Cantley and colleagues Malcolm Whitman, David Kaplan, Tom Roberts, and Brian Schaffhausen made the seminal discovery of **the existence of phosphoinositide-3-kinase (PI3K)**.

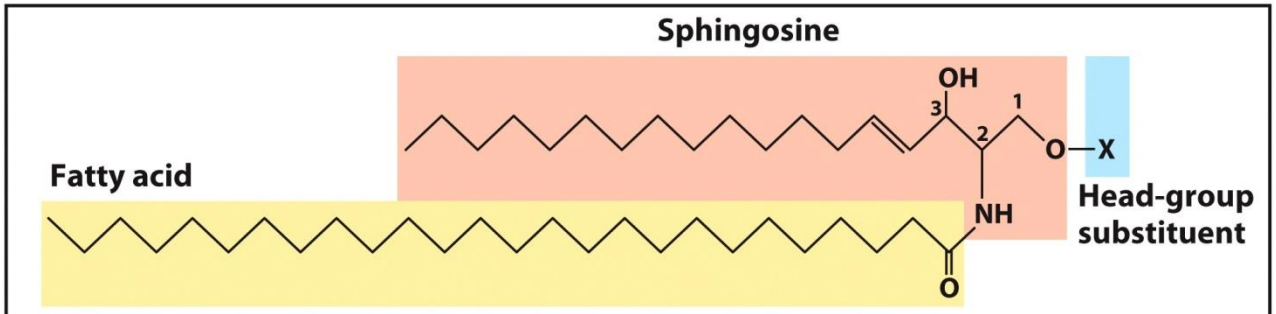
Breakthrough Prize in Life Sciences (2013)
$3,000,000

https://en.wikipedia.org/wiki/Lewis_C._Cantley

- **Sphingolipids (鞘脂)**

  Membrane sphingolipids also can serve as sources of intracellular messengers.

  Both ceramide（酰基鞘氨醇）and sphingomyelin（神经鞘髓磷脂）are potent regulators of protein kinases, and ceramide or its derivatives are known to be involved in the regulation of cell division, differentiation, migration, and programmed cell death (apoptosis).

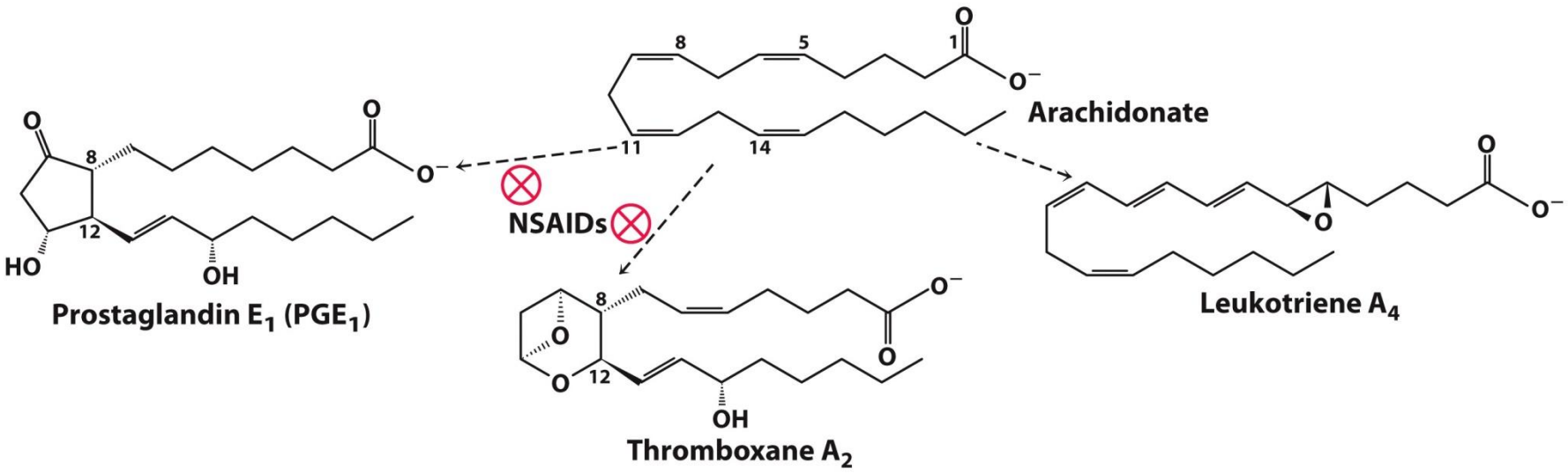


Name of sphingolipid	Name of X—O	Formula of X
Ceramide	—	—H
Sphingomyelin	Phosphocholine	—P(=O)(O⁻)—O—CH₂—CH₂—N⁺(CH₃)₃

Eicosanoids (二十烷类衍生物; 类花生酸)

All eicosanoids are derived from **arachidonic acid** (花生四烯酸；二十碳四烯酸) (20:4($\Delta^{5,8,11,14}$)), the 20-carbon polyunsaturated fatty acid from which they take their general name (Greek *eikosi*, “twenty”).

There are three classes of eicosanoids: **prostaglandins (前列腺素类)**, **thromboxanes (血栓烷素)**, and **leukotrienes (白细胞三烯)**.



Eicosanoids are *paracrine* hormones, substances that act only on cells near the point of hormone synthesis instead of being transported in the blood to act on cells in other tissues or organs.

- **Eicosanoids derivatives have a variety of dramatic effects on vertebrate tissues**
  - **Prostaglandins** (PG)

    Contain a five-carbon ring originating from the chain of arachidonic acid. Their name derives from the prostate gland.

    - **Two groups of prostaglandins**

      PGE (*e*ther-soluble) : PGE1, PGE2, ……

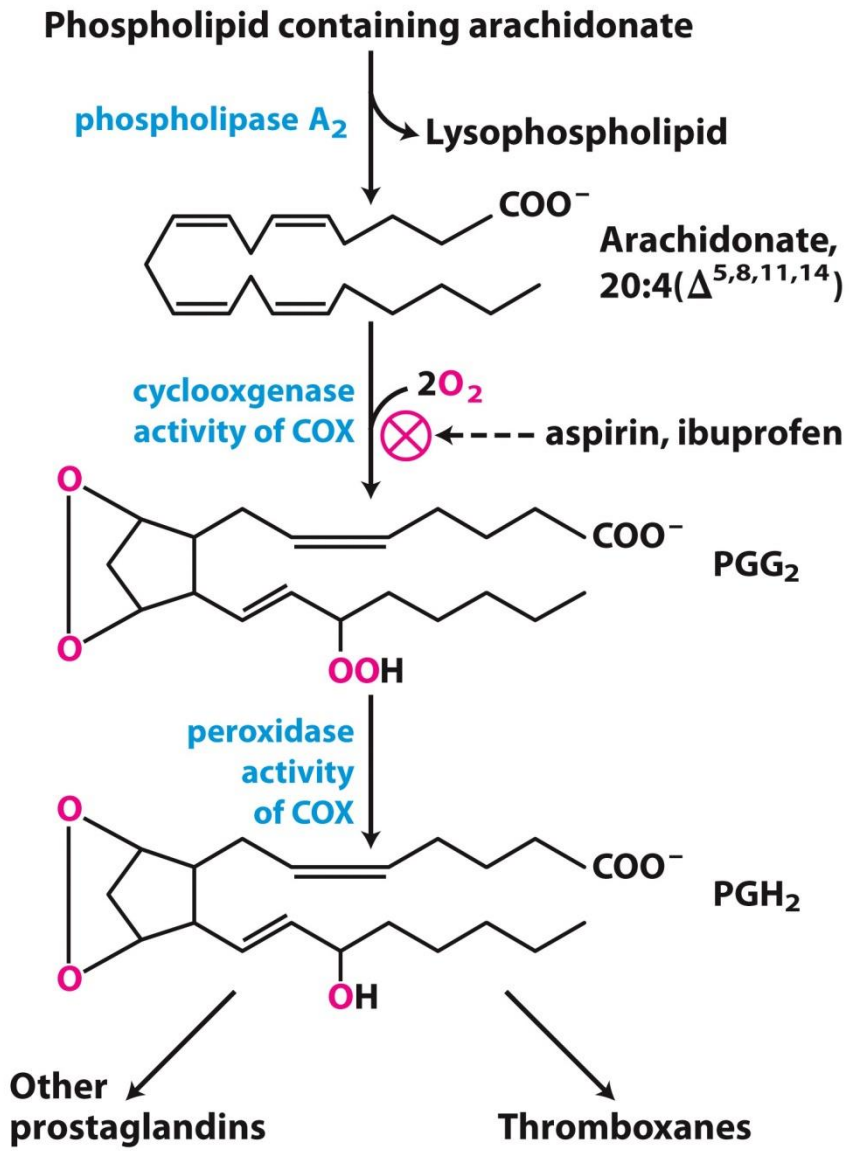
      PGF (*f*osfat (Swedish for phosphate) buffer–soluble) : PGF1, PGF2, ……
    - **Functions of prostaglandins**
      - ✓ Stimulate contraction of the smooth muscle of the uterus during menstruation and labor;
      - ✓ Affect blood flow to specific organs, the wake-sleep cycle, and the responsiveness of certain tissues to hormones such as epinephrine and glucagon;
      - ✓ Prostaglandins in a third group elevate body temperature (producing fever) and cause inflammation and pain;
      - ✓ etc.

Thromboxanes

Have a six-membered ring containing an ether, which are produced by platelets.

- **Functions of thromboxanes**
  Act in the formation of blood clots and the reduction of blood flow to the site of a clot.

The nonsteroidal antiinflammatory drugs (NSAIDs)—aspirin, ibuprofen, and meclofenamate, etc.—inhibit the activity of cyclooxygenase (COX), which catalyzes an early step in the pathway from arachidonate to prostaglandins and thromboxanes.



Leukotrienes

Derived from arachidonic acid and contain three conjugated double bonds. They are first found in leukocytes (white blood cells).

- **Leukotrienes are powerful biological signals**

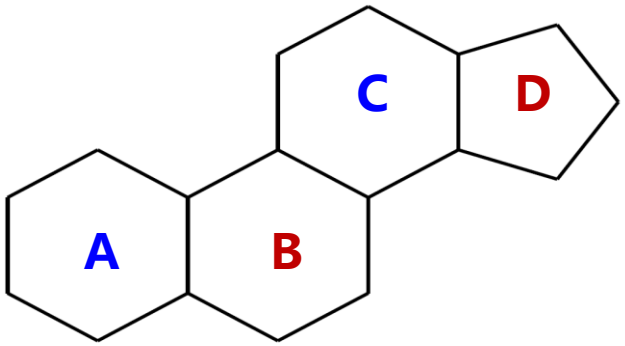
  Leukotrienes induce contraction of the smooth muscle lining the airways to the lung. Overproduction of leukotrienes causes asthmatic attacks.

The strong contraction of the smooth muscle of the lungs that occurs during anaphylactic shock is part of the potentially fatal allergic reaction in individuals hypersensitive to bee stings, penicillin, or other agents.

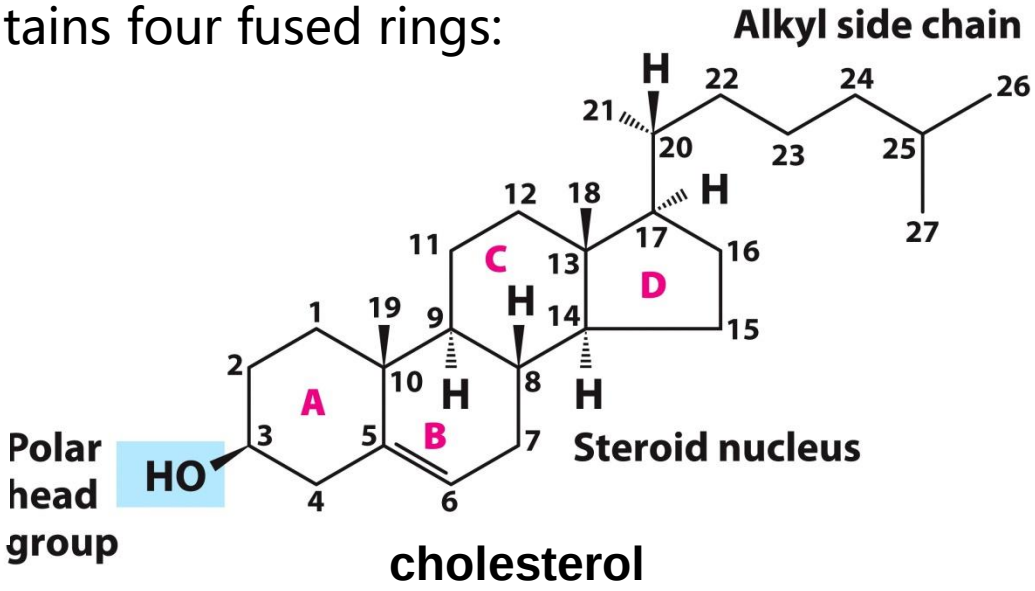
Steroids (类固醇)

Steroids are classified as lipids because they are soluble in nonpolar solvents, but they are non-saponifiable because the components are not held together by ester linkages.

The basic steroid structure contains four fused rings:



steroid ring system



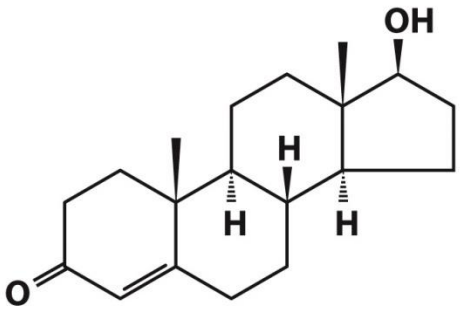
cholesterol

Steroids are oxidized derivatives of sterols; they have the sterol nucleus but lack the alkyl chain attached to ring D of cholesterol, and they are more polar than cholesterol.

- **Steroid hormones carry messages between tissues**

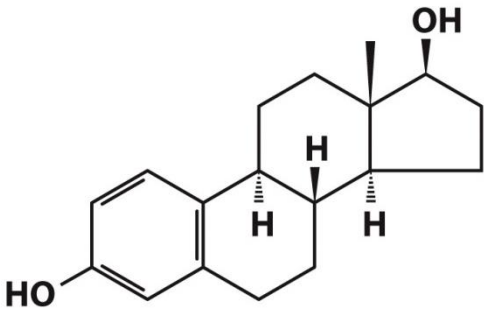
  Steroid hormones move through the bloodstream (on protein carriers) from their site of production to target tissues, where they enter cells, bind to highly specific receptor proteins in the nucleus, and trigger changes in gene expression and thus metabolism.

Sex hormones



Testosterone

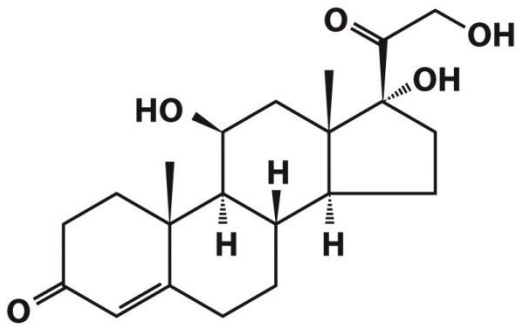
睾丸激素



β-Estradiol

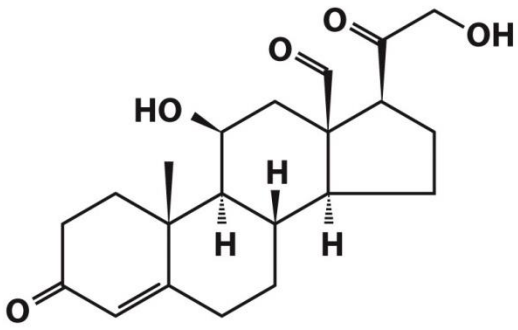
雌二醇

Hormones produced by the adrenal cortex.



Cortisol

皮质醇

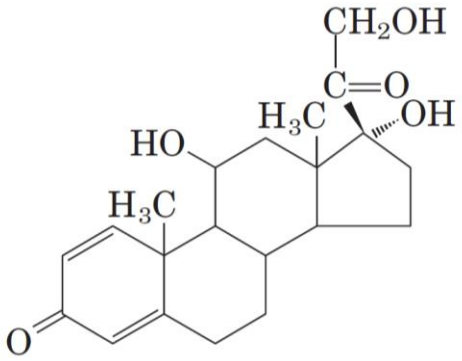


Aldosterone

醛甾酮

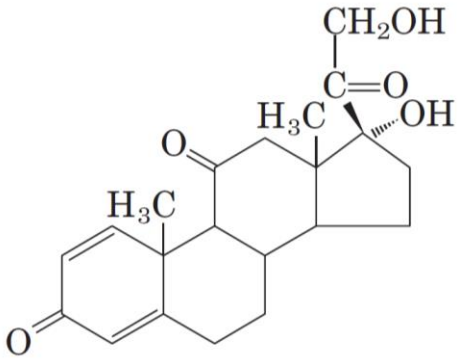
Steroid drugs

Prednisone and **prednisolone** are steroid drugs with potent antiinflammatory activities using for treatment of asthma and rheumatoid arthritis.



Prednisolone

氢化泼尼松

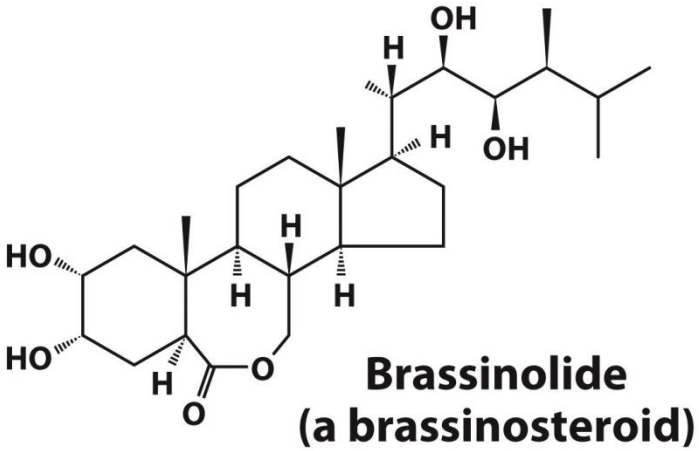


Prednisone

泼尼松

Plants use phosphatidylinositols, steroids, and eicosanoidlike compounds in signaling

- **Brassinolide** and the related group of brassinosteroids are potent growth regulators in plants, increasing the rate of stem elongation and influencing the orientation of cellulose microfibrils in the cell wall during growth.

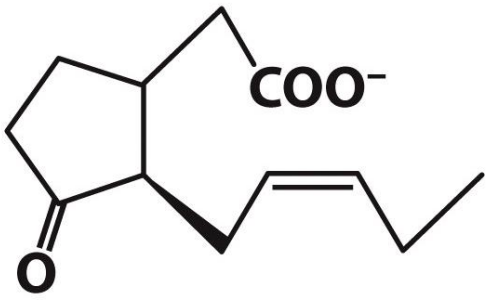


Brassinolide
(a brassinosteroid)

布拉西诺内酯/芸苔甾内酯

- **Plants produce literally thousands of different lipophilic compounds, volatile substances**

Jasmonate, derived from the fatty acid 18:3($\Delta^{9,12,15}$) in membrane lipids, triggers the plant's defenses in response to insect-inflicted damage.



Jasmonate

茉莉酸

The methyl ester of jasmonate gives the characteristic fragrance of jasmine oil, which is widely used in the perfume industry.

These volatile substances are used to attract pollinators, to repel herbivores, to attract organisms that defend the plant against herbivores, and to communicate with other plants.

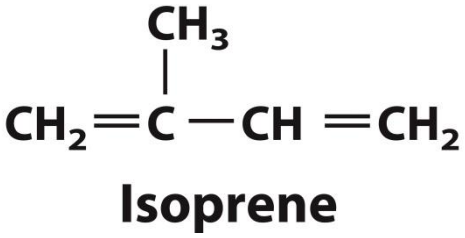
Vitamins

Vitamins are essential to the health of humans and other vertebrates but cannot be synthesized by these animals and must therefore be obtained in the diet.

Fat-soluble vitamins: vitamin groups A, D, E, and K

Water-soluble vitamins: vitamins B and C

The fat-soluble are all isoprenoid (类异戊二烯) compounds synthesized by the condensation of multiple isoprene (异戊二烯) units.

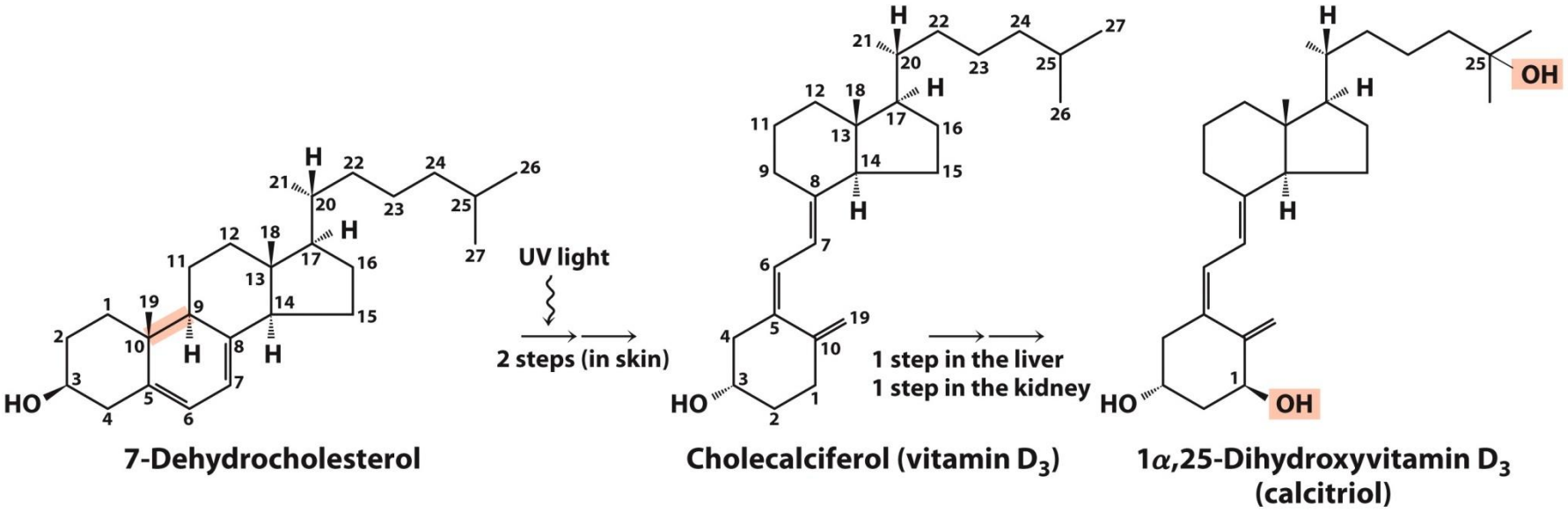


Isoprene

Vitamins D and A serve as hormone precursors.

- **Vitamin D_3 production and metabolism**

  Vitamin D_3, also called **cholecalciferol (**胆钙化醇), is) is produced in the skin by UV irradiation of 7-dehydrocholesterol.



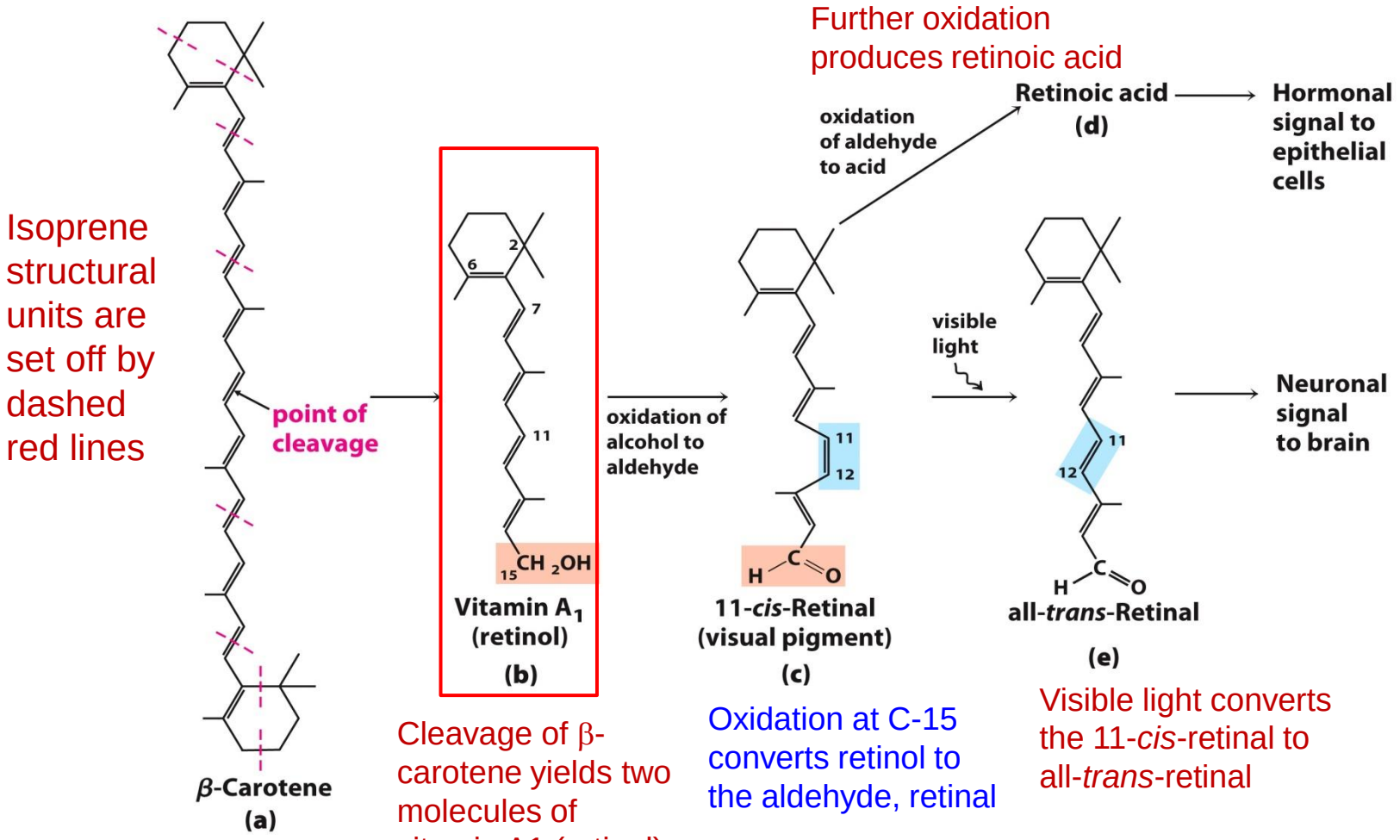
Vitamin D_3 is not itself biologically active. A hydroxyl group is added at C-25 in liver; then a second hydroxylation is added at C-1 in kidney to produce 1α,25-dihydroxyvitamin D_3, the active hormone that regulates calcium uptake in the intestine and calcium levels in kidney and bone. Deficiency of vitamin D leads to defective bone formation and the disease rickets.

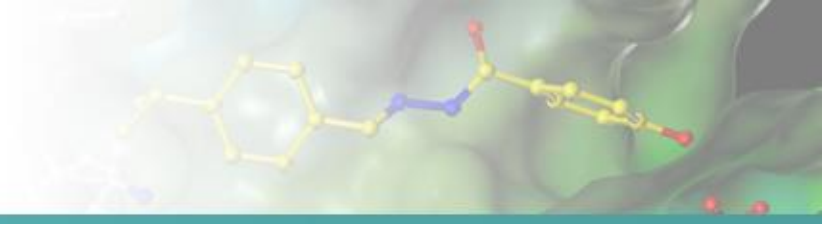
Rickets （佝偻病）

Before vitamin D treatment

After 14 months of vitamin D treatment

- **Vitamin A_1 and its precursor and derivatives**





- **Vitamin A (retinol)**, in its various forms, functions as a hormone and as the visual pigment of the vertebrate eye.

✓ Acting through receptor proteins in the cell nucleus, the vitamin A derivative **retinoic acid** regulates gene expression in the development of epithelial tissue, including skin.

✓ **Retinoic acid** is the active ingredient in the drug tretinoin (Retin-A), used in the treatment of severe acne and wrinkled skin.

✓ **Retinal**（视黄醇）is the pigment that initiates the response of rod and cone cells of the retina to light, producing a neuronal signal to the brain.

Vitamin A was first isolated from fish liver oils; liver, eggs, whole milk, and butter are also good dietary sources. β-carotene in vertebrates can be enzymatically converted to vitamin A.

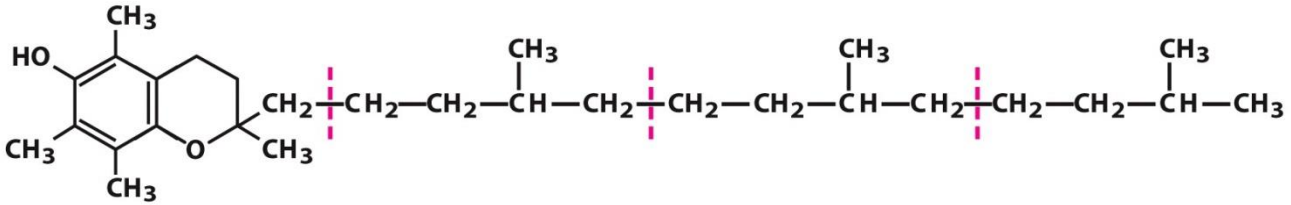
Deficiency of vitamin A leads to a variety of symptoms in humans, including dryness of the skin, eyes, and mucous membranes; retarded development and growth; and night blindness.

- **Vitamins E and K and the lipid quinones are oxidation-reduction cofactors**

Vitamin E is the collective name for a group of closely related lipids called **tocopherols** (生育酚), all of which contain a substituted aromatic ring and a long isoprenoid side chain.

(a)

Vitamin E: an antioxidant

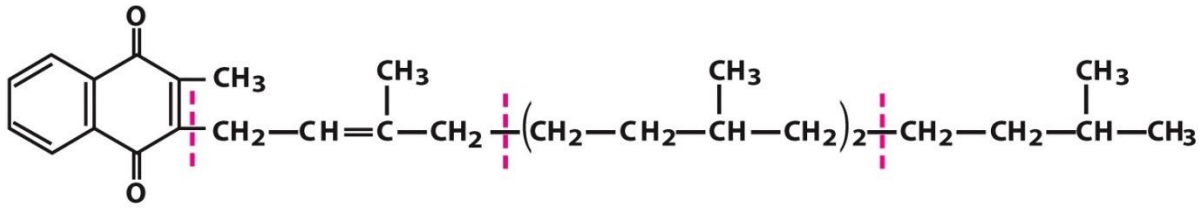


Tocopherols are biological antioxidants. The aromatic ring reacts with and destroys the most reactive forms of oxygen radicals and other free radicals, protecting unsaturated fatty acids from oxidation and preventing oxidative damage to membrane lipids.

Tocopherols are found in eggs and vegetable oils and are especially abundant in wheat germ.

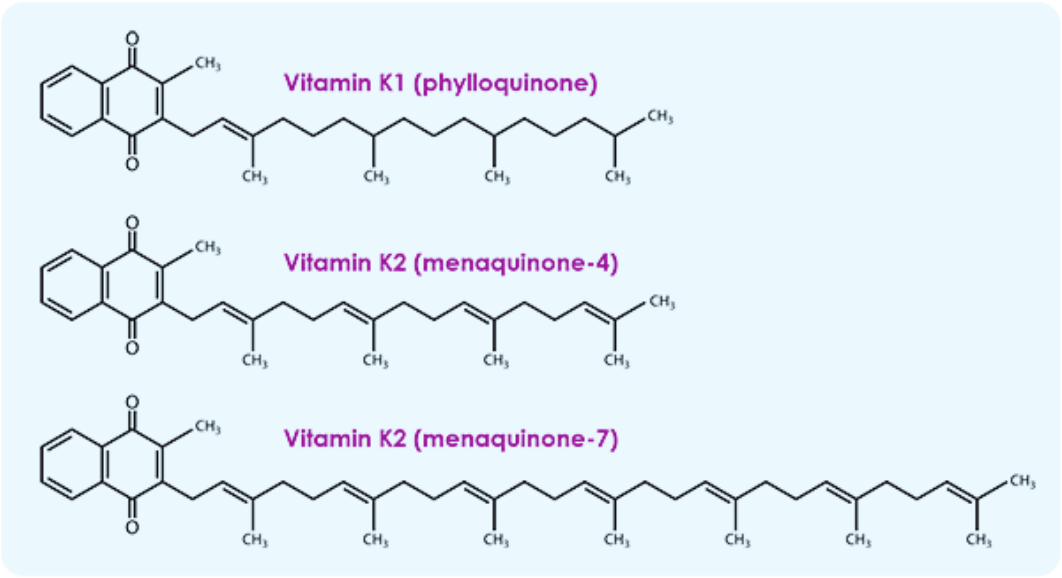
Vitamin K, its aromatic ring under goes a cycle of oxidation and reduction during the formation of active prothrombin (凝血酶原), a blood plasma protein essential in blood clotting.

(b)
Vitamin K_1: a blood-clotting cofactor (phylloquinone)



Prothrombin is a proteolytic enzyme that splits peptide bonds in the blood protein fibrinogen to convert it to fibrin, the insoluble fibrous protein that holds blood clots together.

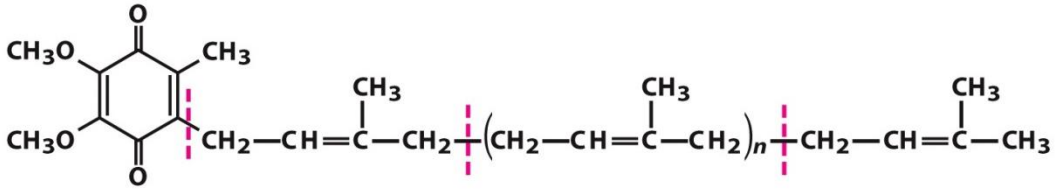
Vitamin K1 (phylloquinone) is found in green plant leaves; a related form, vitamin K2 (menaquinone), is formed by bacteria living in the vertebrate intestine.



Ubiquinone (also called coenzyme Q) and **plastoquinone** are isoprenoids that function as lipophilic electron carriers in the oxidation-reduction reactions that drive ATP synthesis in mitochondria and chloroplasts, respectively. Both ubiquinone and plastoquinone can accept either one or two electrons and either one or two protons.

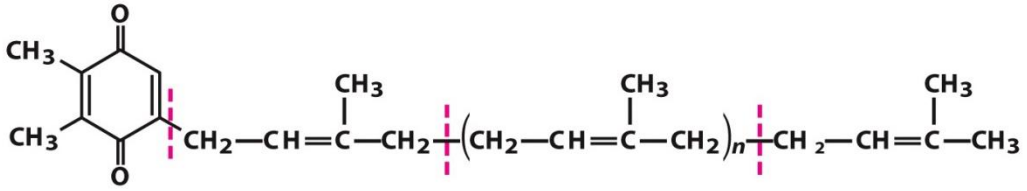
(d)

Ubiquinone: a mitochondrial electron carrier (coenzyme Q) ($n = 4$ to 8)



(e)

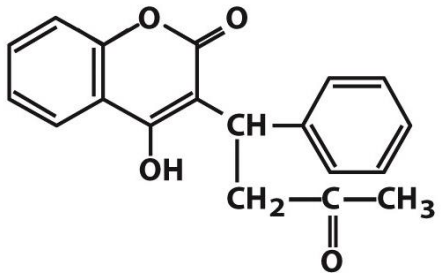
Plastoquinone: a chloroplast electron carrier ($n = 4$ to 8)



Warfarin is a synthetic compound that inhibits the formation of active prothrombin.

(c)

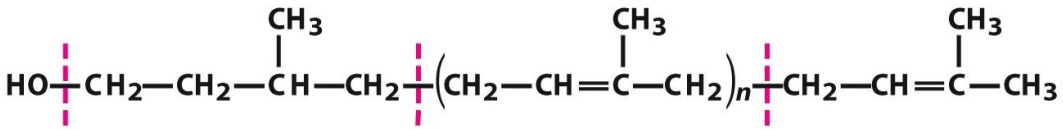
Warfarin: a blood anticoagulant



Dolichols activate sugar precursors for biosynthesis

Dolichols (多萜醇) are isoprenoid alcohols act as sugar carriers during assembly of the complex carbohydrates of bacterial cell walls, and during the addition of polysaccharide units to certain proteins (glycoproteins) and lipids (glycolipids) in eukaryotes. The sugar units to be added are chemically activated by attachment to dolichols.

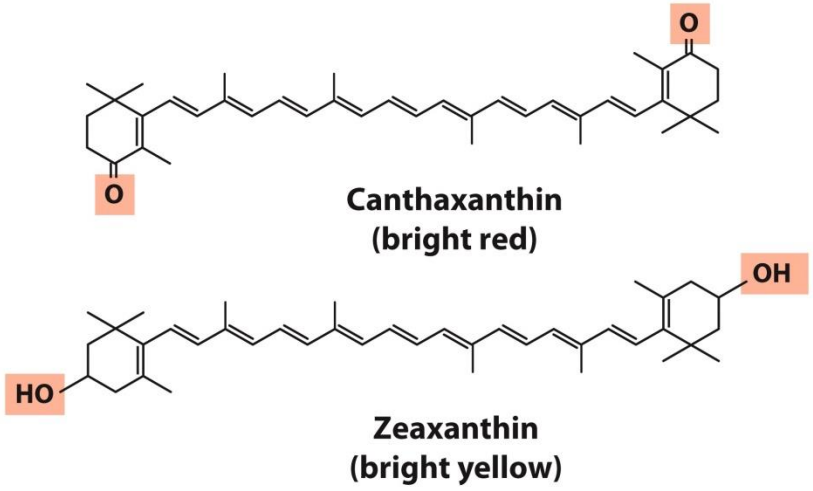
(f)
Dolichol: a sugar carrier
(n = 9 to 22)



These compounds have strong hydrophobic interactions with membrane lipids, anchoring the attached sugars to the membrane, where they participate in sugar-transfer reactions.

Many natural pigments are lipidic conjugated dienes

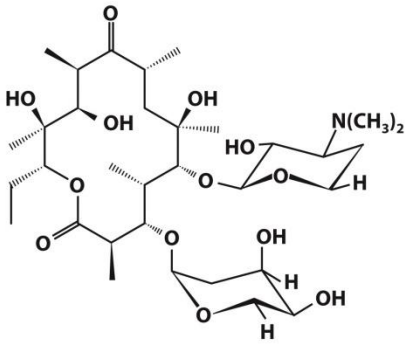
Conjugated dienes (共轭二烯烃) have carbon chains with alternating single and double bonds. Because this structural arrangement allows the delocalization of electrons, the compounds can be excited by low-energy electromagnetic radiation (visible light), giving them colors visible to humans and other animals.



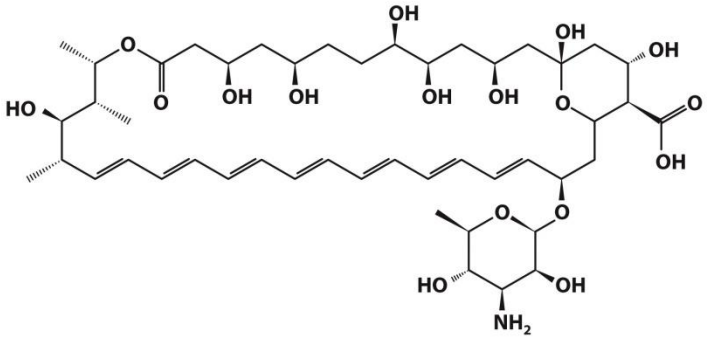
Like sterols, steroids, dolichols, vitamins A, E, D, and K, ubiquinone, and plastoquinone, these pigments are synthesized from five-carbon isoprene derivatives.

Polyketides are natural products with potent biological activities

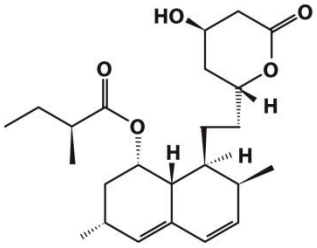
Polyketides (聚酮) are a diverse group of lipids with biosynthetic pathways similar to those for fatty acids. They are **secondary metabolites**, compounds that are not central to an organism's metabolism but that serve some subsidiary function that gives their producers an advantage in some ecological niche.



Erythromycin (antibiotic)



Amphotericin B (antifungal)

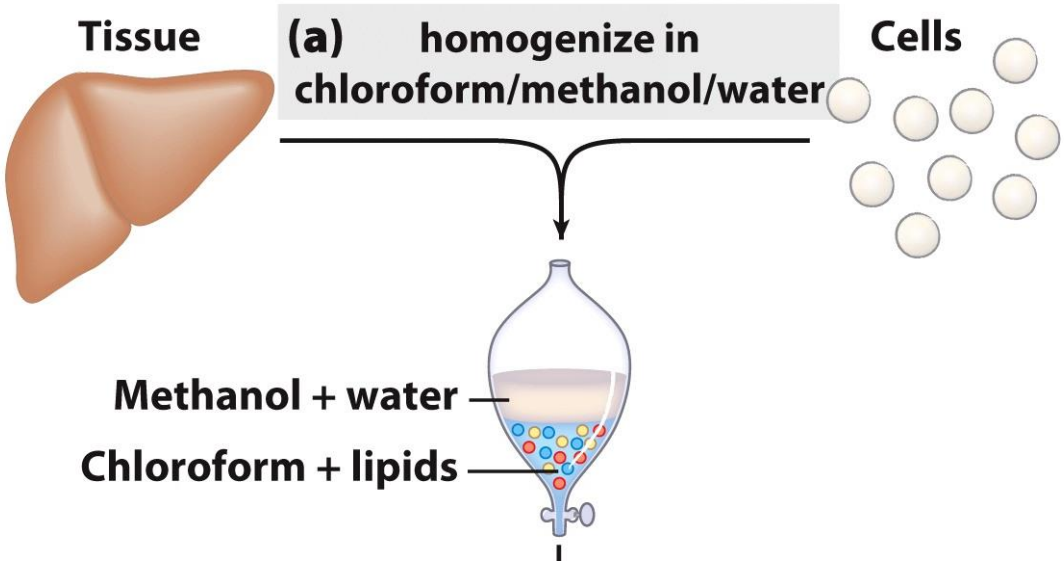


Lovastatin (statin)

Many polyketides find use in medicine as antibiotics (erythromycin), antifungals (amphotericin B), or inhibitors of cholesterol synthesis (lovastatin).

10.4 Working with Lipids

- **Lipid extraction requires organic solvents**



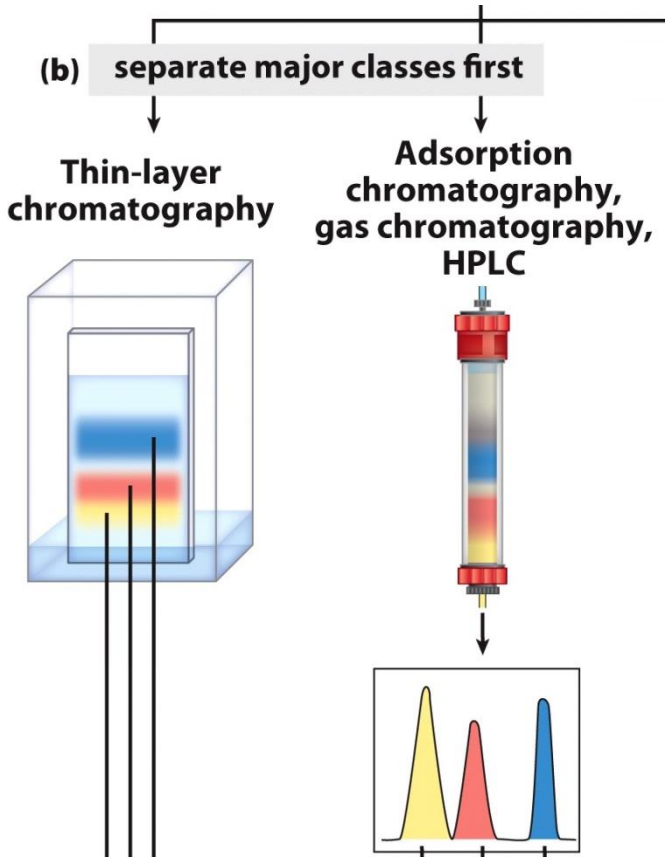
Because lipids are insoluble in water, their extraction and subsequent fractionation require the use of organic. In general, complex mixtures of lipids are separated by differences in polarity or solubility in nonpolar solvents.

- **Adsorption chromatography separates lipids of different polarity**

Complex mixtures of tissue lipids can be fractionated by chromatographic procedures based on the different polarities of each class of lipid.

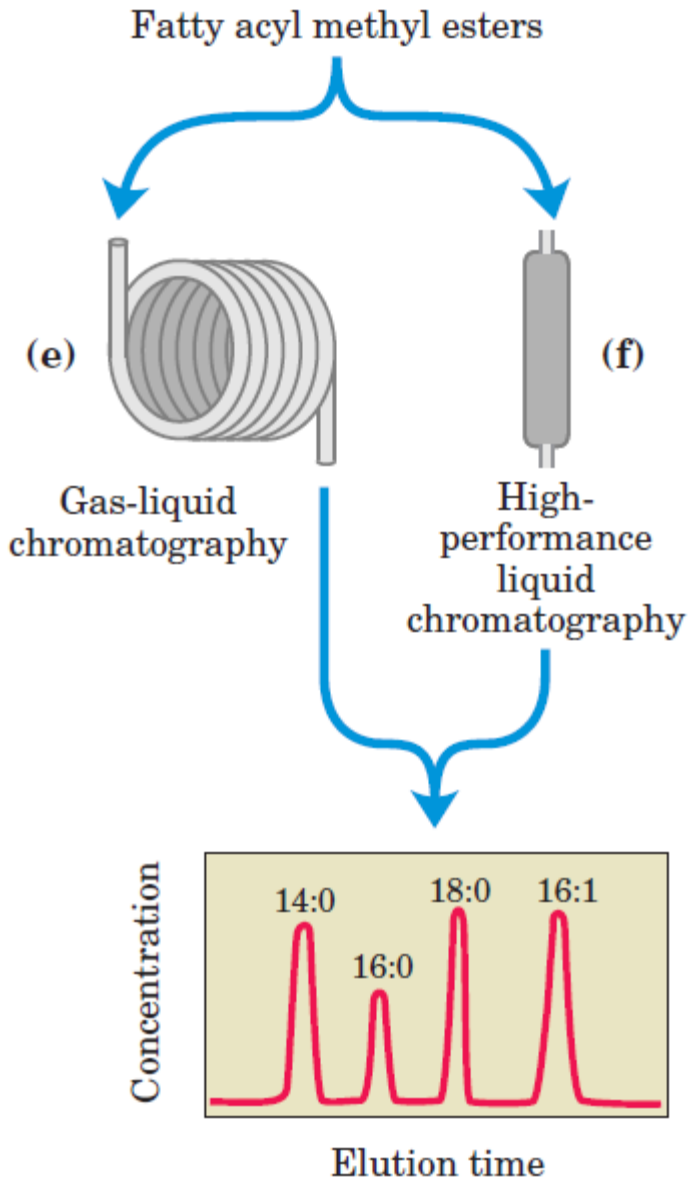
Adsorption chromatography

Thin-layer chromatography



- **Gas-liquid chromatography resolves mixtures of volatile lipid derivatives**

Gas-liquid chromatography separates volatile components of a mixture according to their relative tendencies to dissolve in the inert material packed in the chromatography column or to volatilize and move through the column, carried by a current of an inert gas such as helium.



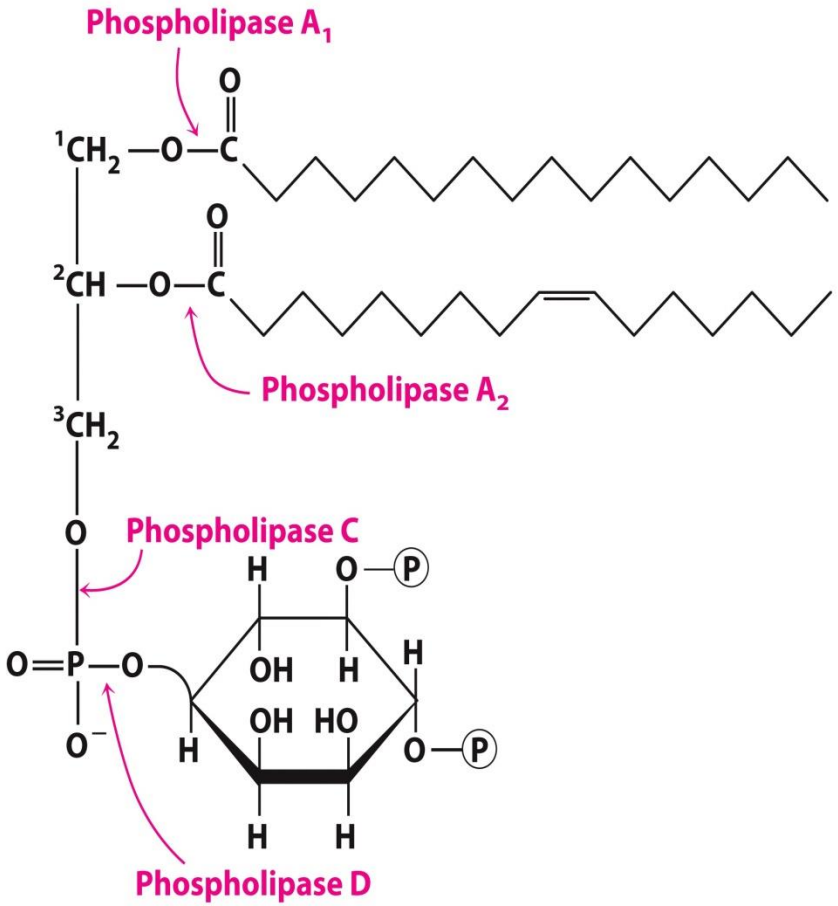
Specific hydrolysis aids in determination of lipid structure

- Certain classes of lipids are susceptible to degradation under specific conditions.

✓ Ester-linked fatty acids in triacylglycerols, phospholipids, and sterol esters are released by mild acid or alkaline treatment.

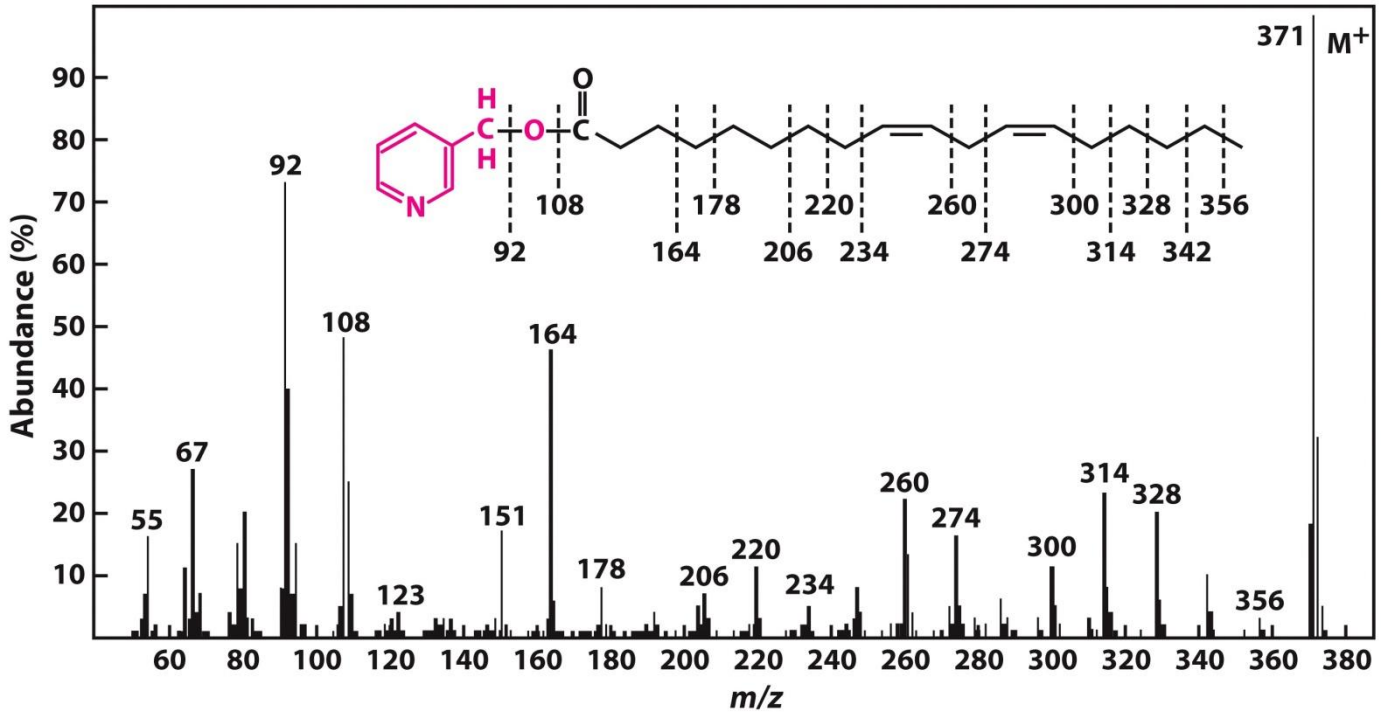
✓ Enzymes that specifically hydrolyze certain lipids are also useful in the determination of lipid structure.

The combination of specific hydrolysis with characterization of the products by thin-layer, gas-liquid, or high-performance liquid chromatography often allows determination of a lipid structure.



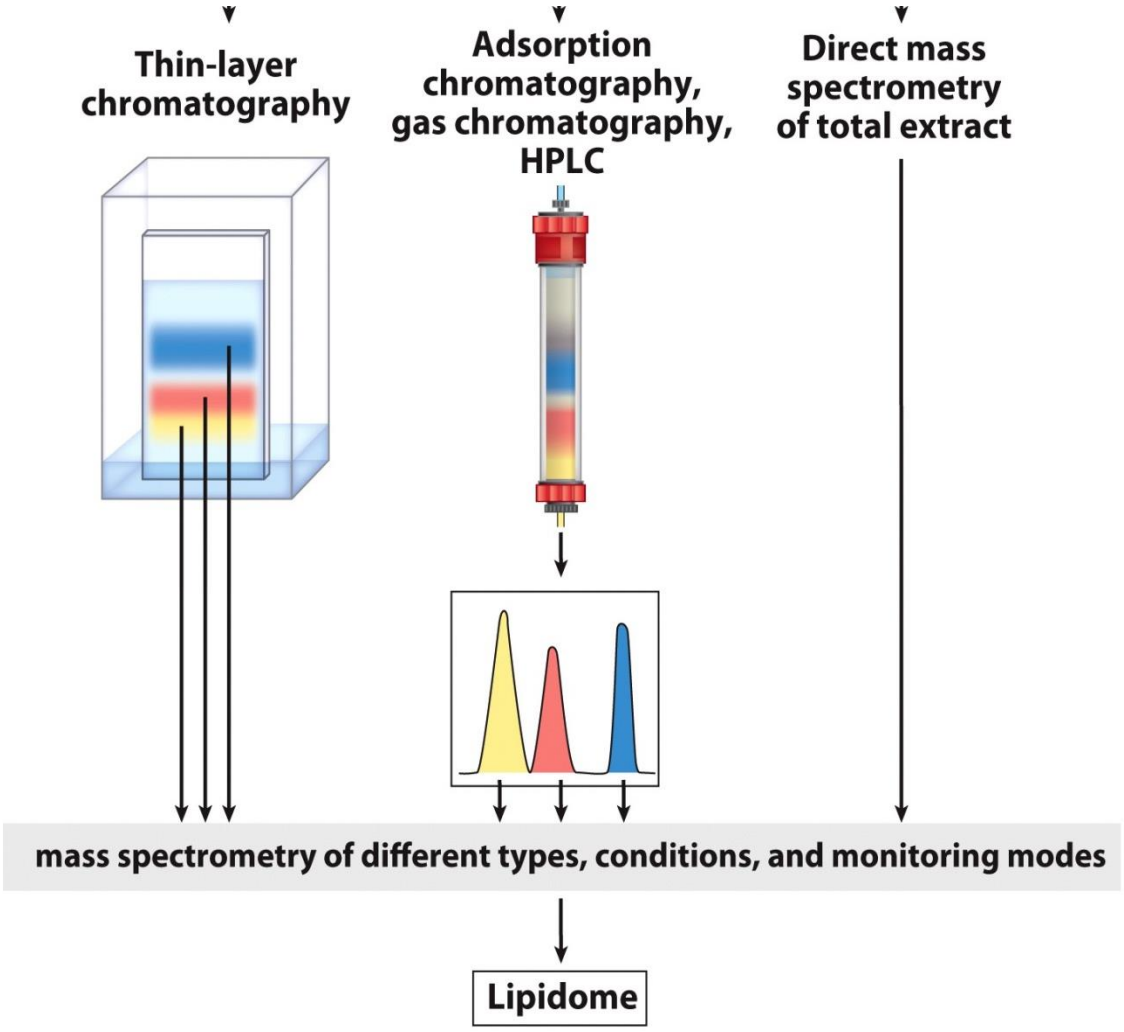
Phosphatidylinositol 4,5-bisphosphate

- **Mass spectrometry reveals complete lipid structure**



Lipidomics seeks to catalog all lipids and their functions

An animal cell contains more than a thousand different lipid species, each presumably having a specific function. The application of mass spectrometric techniques with high throughput and high resolution can provide quantitative catalogs of all the lipids present in a specific cell type under particular conditions—the **lipidome**.



Take home messages …

Active Lipids: Lipids as Signals, Cofactors, and Pigments

- ✓ Some types of lipids, although present in relatively small quantities, play critical roles as cofactors or signals.
- ✓ Prostaglandins, thromboxanes, and leukotrienes (the eicosanoids), derived from arachidonate, are extremely potent hormones.
- ✓ Steroid hormones, derived from sterols, serve as powerful biological signals, such as the sex hormones.
- ✓ Vitamins D, A, E, and K are fat-soluble compounds made up of isoprene units, all play essential roles in the metabolism or physiology of animals.