ANSC/NUTR 618
Lipids & Lipid Metabolism
Prostaglandins and Leukotrienes

I. Nonessential fatty acids

A. Synthesized completely by the fatty acid synthase reaction (e.g., myristic and palmitic acid).

B. Produced by the modification of enzymes produced by the fatty acid synthase reaction (e.g., stearic acid via elongation and oleic acid via desaturation).

C. Derived from the modification of dietary essential fatty acids (e.g., arachidonic acid, which is derived from linoleic acid).

II. Essential fatty acids

A. Definition: Essential fatty acids are those that are:

1. ***Not*** synthesized by animals (vertebrates or invertebrates) (esp. linoleic and α-linolenic acid).

2. Are required only during periods of fetal and/or rapid growth (i.e., ***conditionally essential***) (e.g., docosahexaenoic acid during fetal growth).

B. Sources

1. Linoleic acid (18:2n-6) is found primarily in plant sources.

2. α-Linolenic acid (18:3n-3) is found primarily in plant sources.

3. Eicosapentanoic acid (20:5n-3) and docosahexaenoic acid (22:6n-3) are found primarily in fish oils.

III. Metabolism of essential fatty acids

A. Plants

1. Synthesize palmitic acid via fatty acid synthase.
2. Fatty acids are esterified into plant phospholipids.
3. Fatty acids are desaturated by Δ9, Δ12, and Δ15 desaturases.

B. Phytoplankton

1. α-Linolenic acid is desaturated and elongated to EPA and DHA.
2. Zooplankton consumed by fish, and their fatty acids enter the food chain.

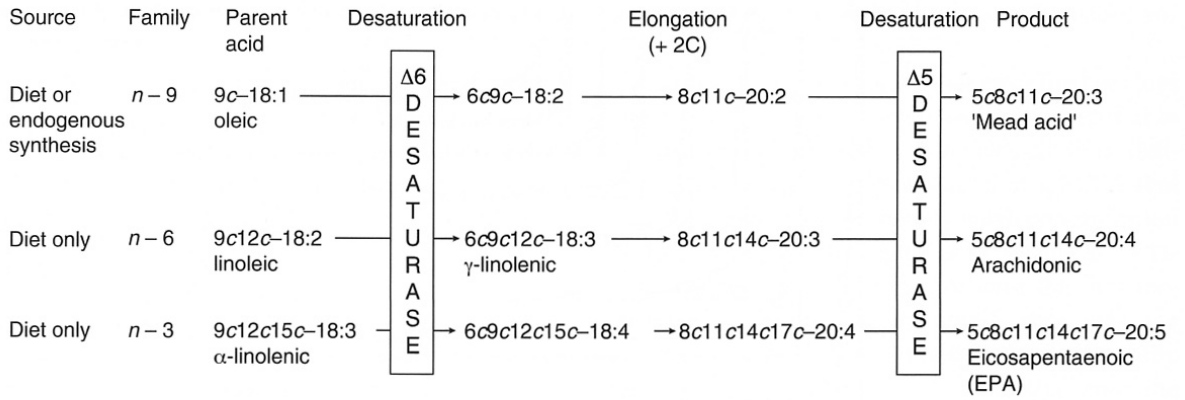


Fig. 4.4 Principal metabolic pathways for desaturation and elongation of 'parent acids' to long-chain polyunsaturated fatty acids in the *n*-9, *n*-6 and *n*-3 families. A minor family, *n*-7 (whose 'parent' acid is palmitoleic acid, 9*c*-16:1) has been omitted for simplicity. As far as we know it has little nutritional significance. The figure aims mainly to illustrate the sequence of alternate desaturations and elongations of the parent acids in each family and the competition between families for the Δ5 and Δ6-desaturases. For example, it should be readily apparent how the Mead acid accumulates in preference to arachidonic acid when there is a dietary deficiency of 18:2*n*-6 and an excess of 18:1*n*-9. An important continuation of the *n*-3 pathway via further elongation to C22 and further metabolism to form docosahexaenoic acid (DHA, 22:6*n*-3) has also been omitted. It is important to note that a 4-desaturase has not been identified and current understanding of the pathway to 22:6*n*-3 is discussed in Section 2.2.5.3.

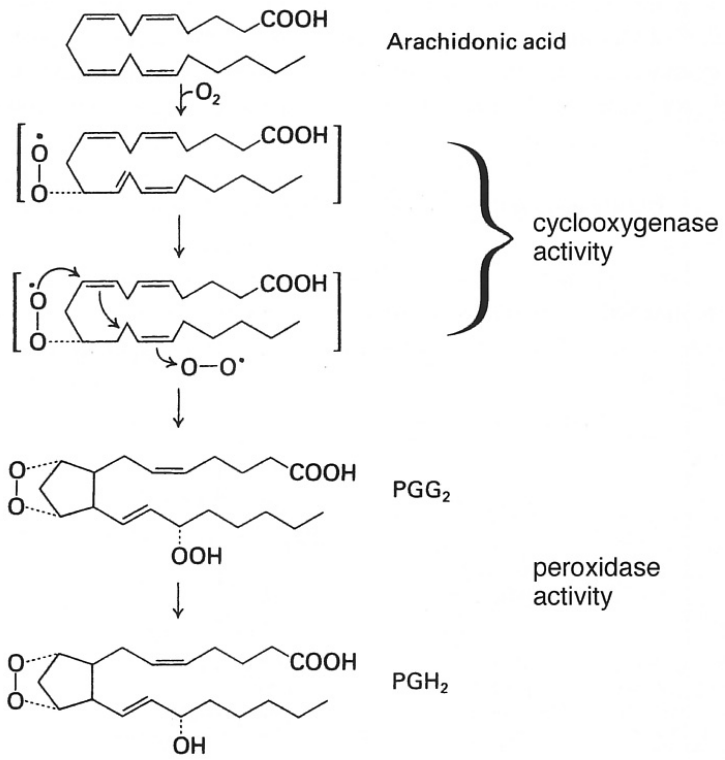
IV. Synthesis of prostaglandins

A. Cyclooxygenase forms pentane ring.

B. Peroxidase converts hydroperoxide to alcohol group.

C. Substrates are *bis* homo-γ-linolenic acid (20:3n-6), arachidonic acid (20:4n-6), and eicosopentanoic acid (20:5n-3).

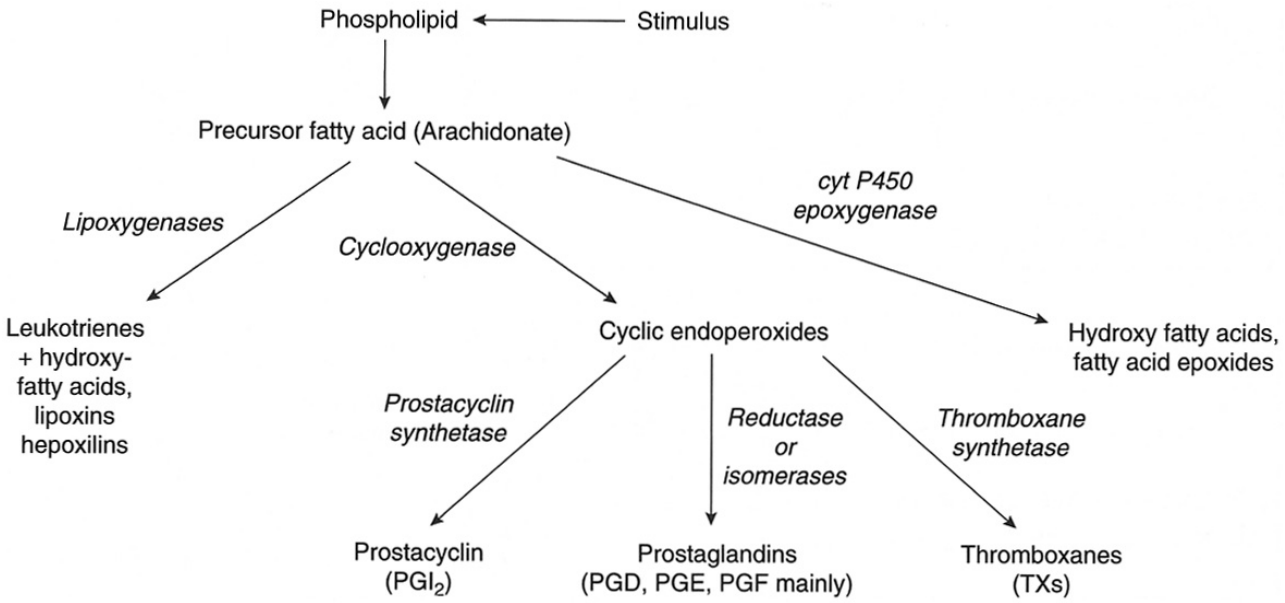
D. Conversion to prostaglandins always eliminates two double bonds.

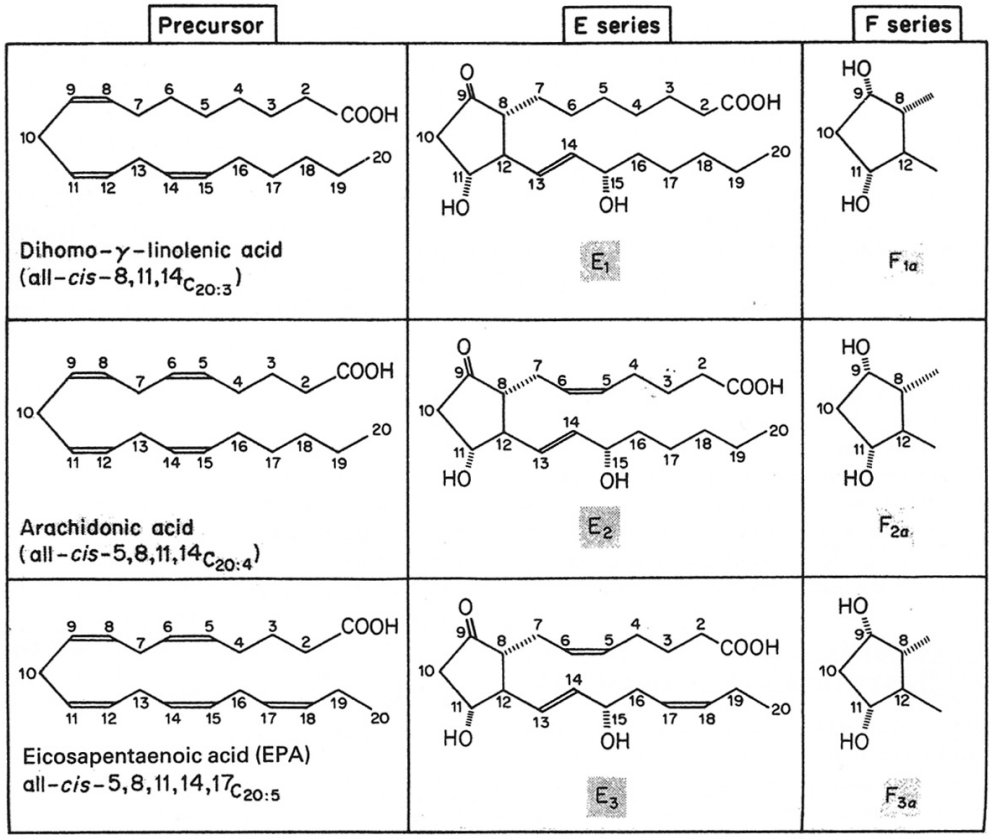


VI. Types of prostaglandins

A. Products of PGH_2

1. PGE_2 (primary product in most tissues); leads to inflammation.
2. Thromboxane (from platelets); necessary for blood clotting.
3. Prostacyclin (from vascular endothelial cells); inhibits blood clotting.





B. Products of the lipooxygenase pathway

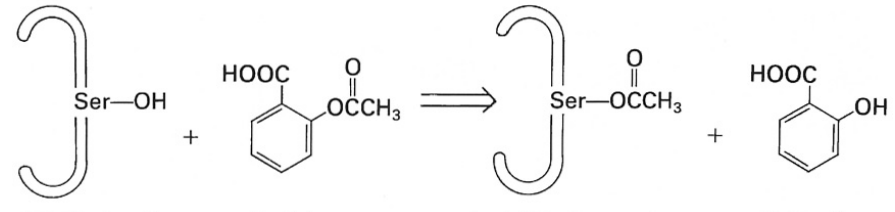
1. Leukotrienes (esp. LTB_4)
2. Slow-reacting substances of anaphylaxis (SRS-A)

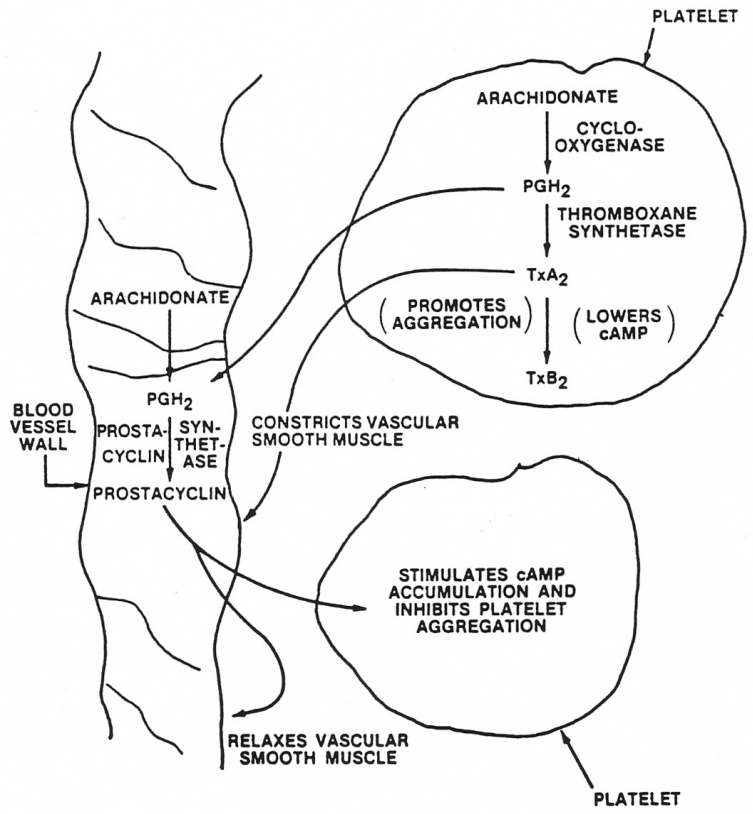
C. Actions of prostaglandins

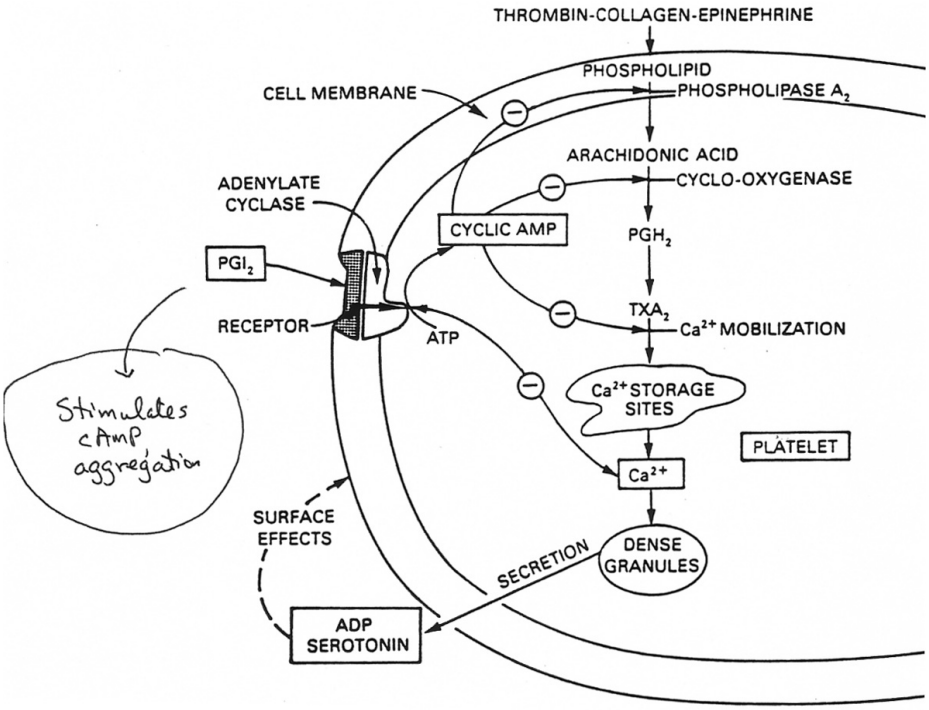
1. Female reproductive system
   a. Steroidogenesis
   b. Ovulation
   c. Regression of the corpus luteum
   d. Menstruation
   e. Parturition
2. Gastric secretion
3. Blood pressure (via effects on kidneys)
4. Pain and inflammation
5. Fever
6. Blood clotting
   a. Thromboxanes
      1) Synthesized in platelets (substrate = phospholipid 20:4n-6).
      2) Promote platelet aggregation.
   b. Prostacyclins
      1) Produced endothelial cells of artery wall.
      2) Inhibit clotting.

D. Action of aspirin

1. Aspirin (acetyl salicylic acid) binds irreversibly to a serine residue on the endoperoxide synthase.
2. The serine residue is acetylated, releasing salicylic acid.
3. New endoperoxide synthase must be synthesized (aspirin is a suicide inhibitor).




PLATELET
ARACHIDONATE
CYCLO-OXYGENASE
PGH2
THROMBOXANE SYNTHETASE
TxA2
PROMOTES AGGREGATION
LOWERS cAMP
TxB2
ARACHIDONATE
PGH2
BLOOD VESSEL WALL
PROSTA-CYCLIN
SYN-THET-ASE
PROSTACYCLIN
CONSTRICTS VASCULAR SMOOTH MUSCLE
STIMULATES cAMP ACCUMULATION AND INHIBITS PLATELET AGGREGATION
RELAXES VASCULAR SMOOTH MUSCLE
PLATELET


THROMBIN-COLLAGEN-EPINEPHRINE
PHOSPHOLIPID
PHOSPHOLIPASE A2
CELL MEMBRANE
ARACHIDONIC ACID
CYCLO-OXYGENASE
ADENYLATE CYCLASE
CYCLIC AMP
PGH2
PGI2
TXA2
Ca2+ MOBILIZATION
RECEPTOR
ATP
Stimulates cAMP aggregation
Ca2+ STORAGE SITES
PLATELET
Ca2+
SURFACE EFFECTS
SECRETION
DENSE GRANULES
ADP SEROTONIN

VII. Leukotrienes

A. General

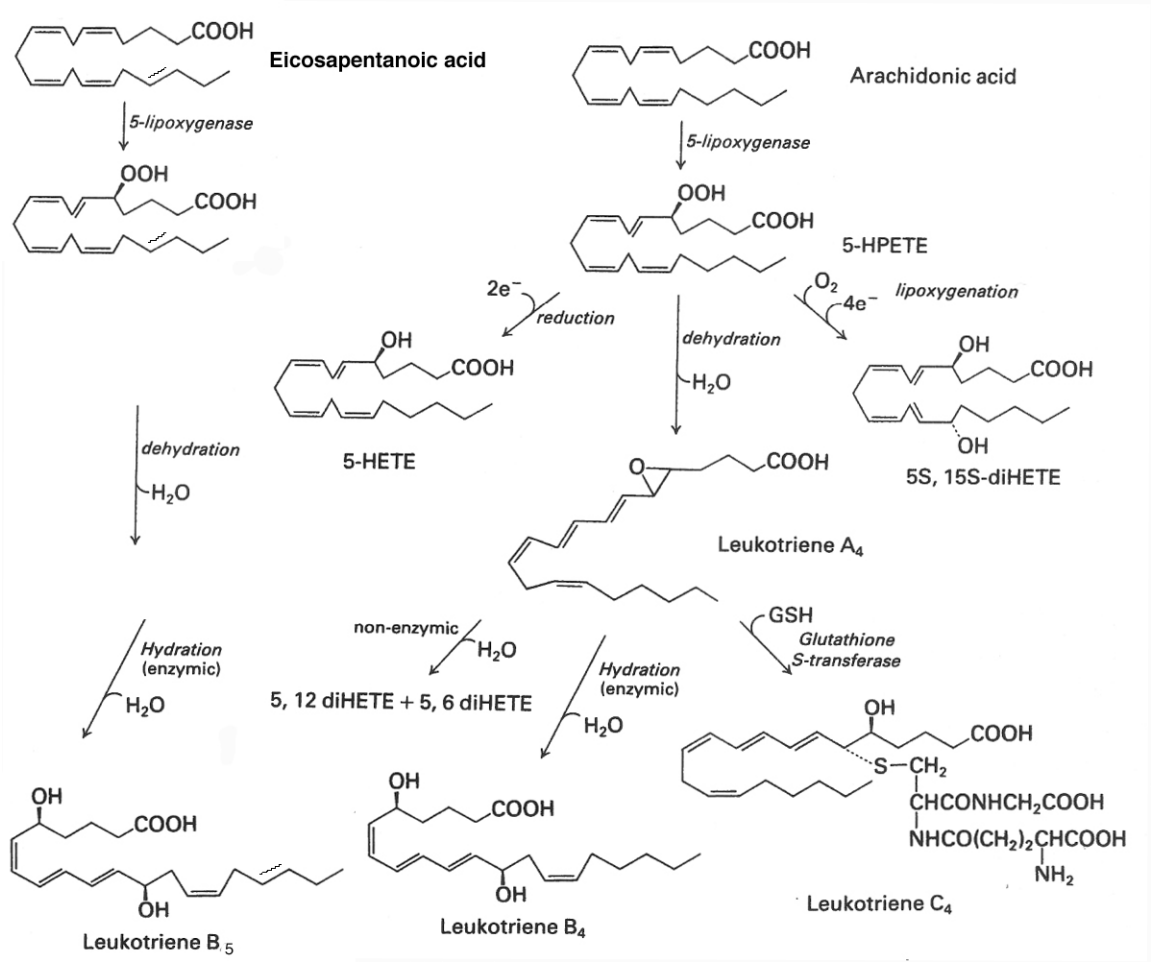
1. 20-carbon
2. Hydroxypolyenoic acids

B. Examples

1. Leukotrienes (esp. LTB_4)
2. Slow-reacting substances of anaphylaxis (SRS-A = LTC_4 and LTD_4)

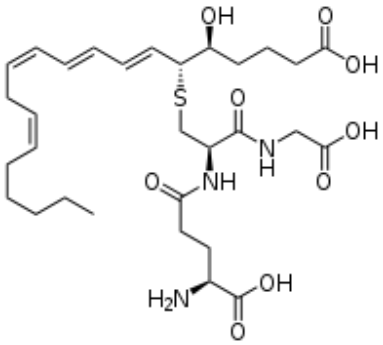
C. Biosynthesis

1. Substrates:
   a. *bis* homo-γ-linolenic acid, C20:3 $\Delta^{8,11,14}$
   b. Arachidonic acid, C20:4 $\Delta^{5,8,11,14}$
   c. Eicosapentanoic acid, C20:5 $\Delta^{5,8,11,14,17}$

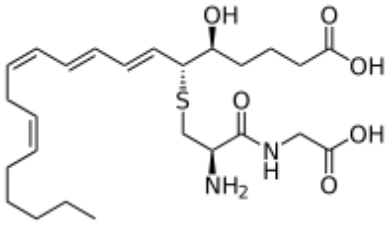


2. Source of substrates
    a. Membrane-bound phospholipids
    b. Arachidonic acid or eicopentanoic acid are released by action of phospholipase A_2
3. SRS-A also incorporate:
    a. Glutathione
    b. Cysteinylglycine
    c. Cysteine

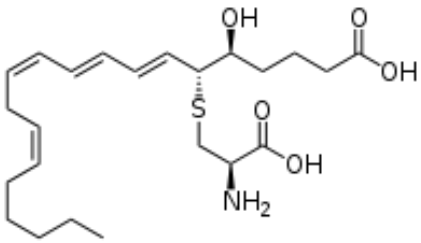
D. Actions of eicosanoids
1. Chemotaxis (slow mobility of leukocytes)
2. Chemokinesis (stimulate migration of leukocytes)
3. SRS-As cause contraction of bronchiolar and tracheal smooth muscle.
    a. Secreted by mast cells, inducing inflammation.
    b. Causes contraction of smooth muscle.
    c. Has a major bronchoconstrictor role in asthma.
    d. 5,000 x more potent than histamine as a bronchoconstictor.



Slow reacting substances of anaphylaxis LTC_4



SRS A LTD_4



SRS LTE_4

VIII. Competition between PGE_2 and PGE_3