

Phospholipid and Eicosanoid Metabolism

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BCH 6206

Chapter 25 pgs 959-981

Topics for Phospholipid and Prostaglandin Metabolism

- ! Triglyceride Biosynthesis
- ! Phospholipid Biosynthesis
 - \$ Evidence for Channeling
- ! Arachidonic Acid Metabolism: the eicosanoids (20carbons)
- ! Eicosanoid regulation
 - \$ Phospholipase A₂
 - \$ PGH₂ Synthase (COX family)
 - \$ NSAIDS

Figure 1

Triglyceride Biosynthesis

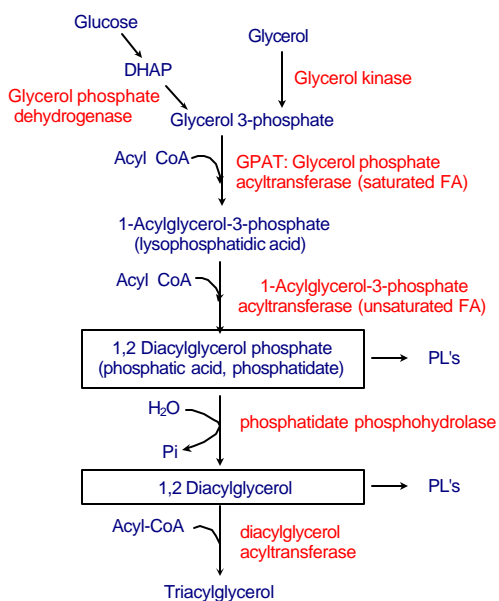


Figure 2

Phosphatidylinositol Synthesis

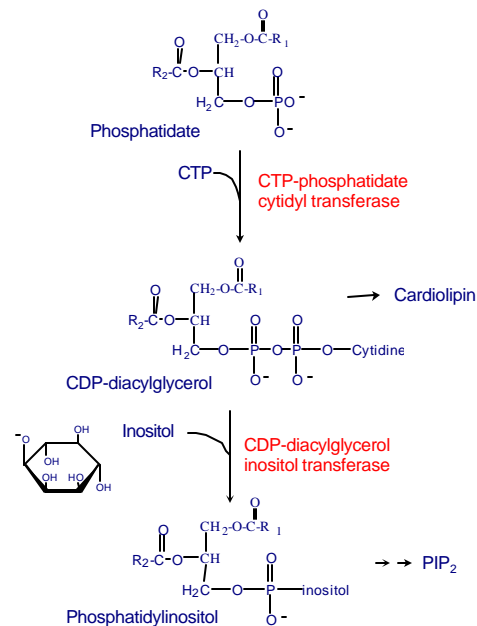


Figure 3

Cardiolipin Biosynthesis

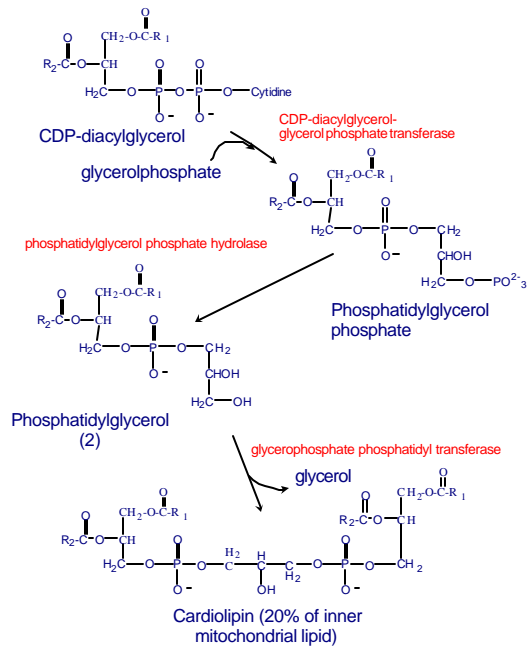


Figure 4

Phosphatidylethanolamine (choline) Biosynthesis

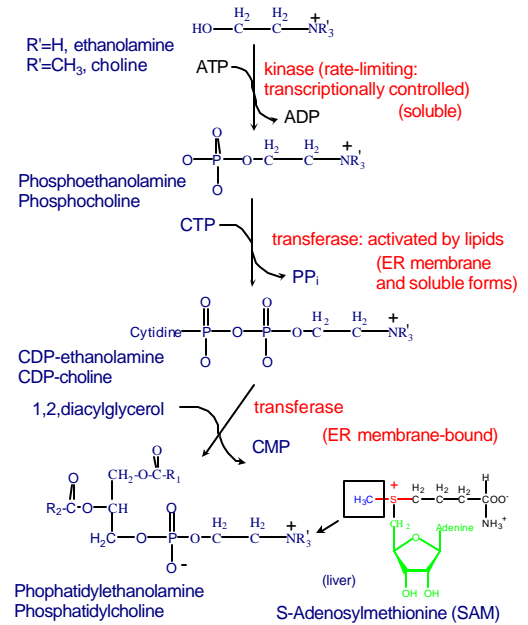


Figure 5

Phosphatidylserine Biosynthesis

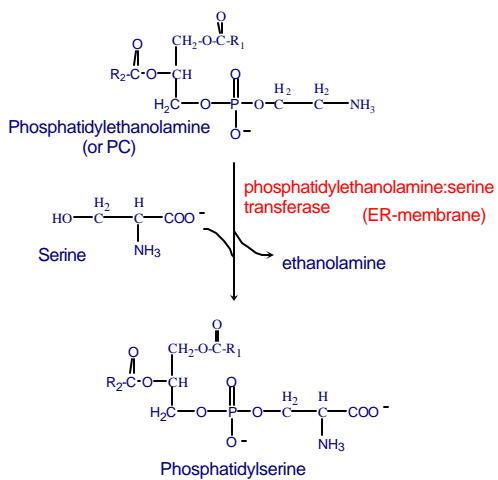


Figure 6

Sphingomyelin Synthesis

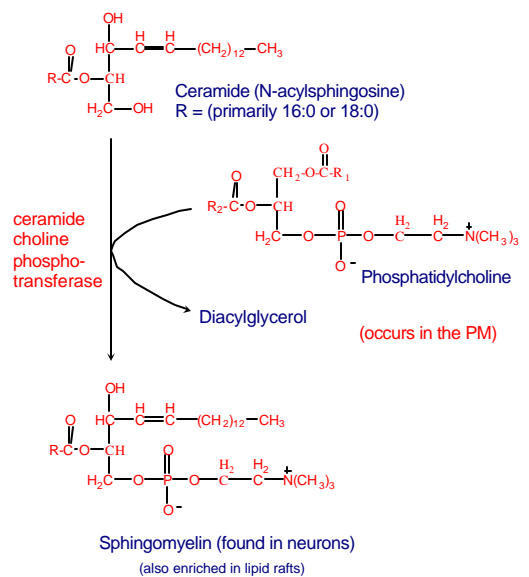
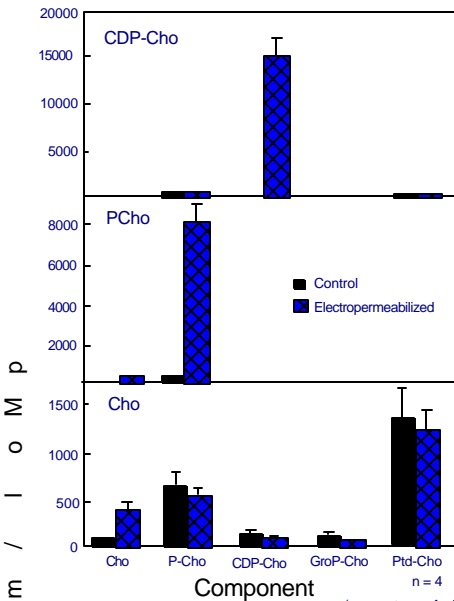


Figure 7

Does Channeling Play a Role in PC Biosynthesis?



adapted from Kent et al. (1991)

(see next page for legend)

Figure 8

Does Channeling Play a Role in PC Biosynthesiscontinued

Figure Legend: Incorporation of [^3H]-methyl choline, [methyl- ^{14}C]phosphocholine, and CDP-[methyl- ^{14}C]choline in control and electropermeabilized C6 glioma cells.

Electroporation was done at 2kV, 0.5uF. Permeabilized cells were then incubated for 2h with either labeled methylcholine (28uM), phosphomethylcholine (300uM), or CDP-methyl choline (300uM). Lipid and water soluble products were separated by solvent partition followed by thin-layer chromatography. The label in the upper left of each panel represents the radiolabeled component added to the cells. The label on the X-axis is the cellular component that became labeled during the incubation. Cho, choline; PCho, phosphocholine; CDP-Cho, CDP-choline; GroPCho, glycerophosphocholine; PtdCho, phosphatidylcholine.

adapted from Kent et al. (1991)

Figure 9

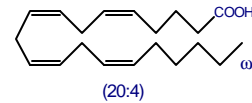
Phospholipid Transfer Proteins

1. Able to catalyze *in vitro* a one for one exchange of specific phospholipids between either natural or artificial phospholipid bilayers by acting as carriers of phospholipid monomers.
2. Three classes have been identified
 - a. specificity for PC
 - b. specificity for PI and PC
 - c. specificity for FAs, cholesterol, and PLs
3. Molecular weight range of these proteins is 28,000 to 35,000 Daltons.

Figure 10

Arachidonic Acid Metabolism (5,8,11,14-eicosatetraenoic acid)

"Cyclic" Arachidonic Acid \longrightarrow Prostaglandins



"Linear" Arachidonic Acid \longrightarrow Leukotrienes

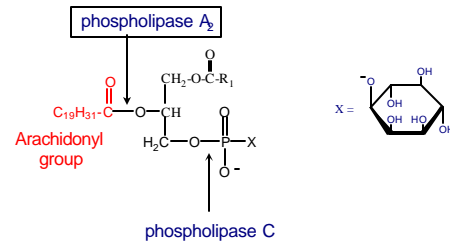
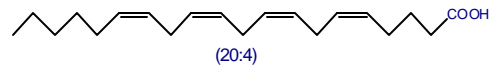
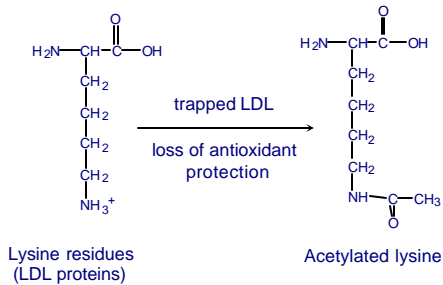


Figure 11a

Development of Atherosclerosis

Essentially a response to injury

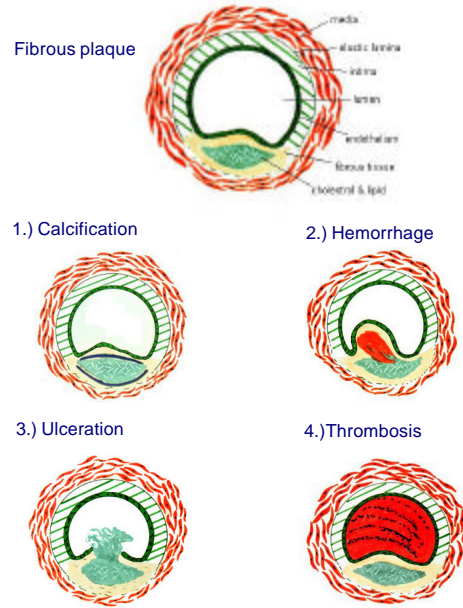
Macrophages (a phagocytic white blood cell) do not express LDL receptor. However, when the apoproteins become oxidized, the macrophage will "endocytose" the oxidized LDL particle using a "scavenger receptor". The cholesterol in the LDL particle is converted to cholesteryl esters...which form the pasty yellow deposit in "atheromas". These can lead to blood clots which stops blood flow causing tissue death...myocardial infarction.



Oxidized fatty acids, released by phospholipase A₂ within LDL particles, mimic the effect of acetylation.

Figure 11b

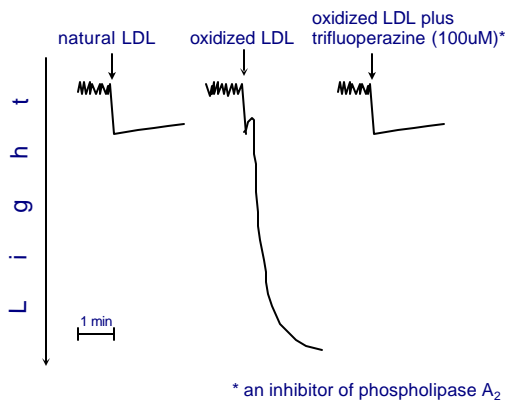
Atheromas



<http://medweb.bham.ac.uk/http/depts/path/Teaching/foundat/athero/athero4.htm>

Figure 11c

Oxidized LDL causes Aggregation of Platelets via Activation of PLA₂



Legend: Tracings show effect of oxidized LDL on platelet aggregation: Suspensions of washed platelets were incubated at 37°C and stirred for 1 minute in an aggregometer. Natural or oxidized human LDL was added as indicated. Tracings representative of 10 different experiments.

adapted from Weidmann et al. (1995)

Figure 12

Prostaglandin H₂ Synthesis

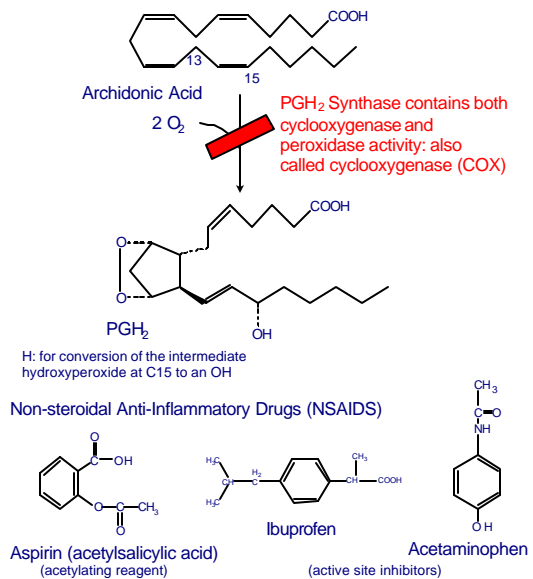
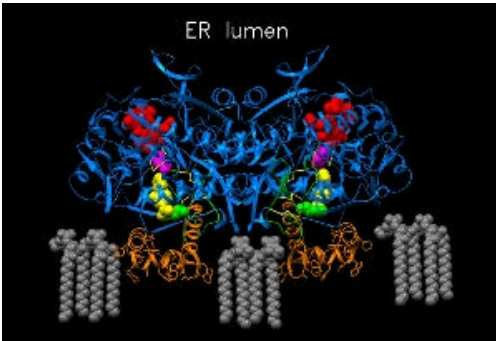


Figure 13

Crystal Structure of PGH₂ synthase

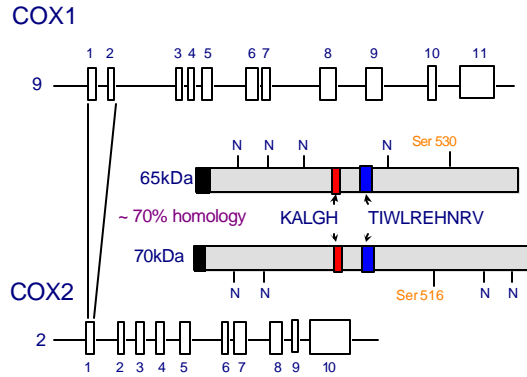


The membrane binding region is in orange. The catalytic domain is in blue. The heme group is in red. Fluriprofen (an ibuprofen analog) is in yellow. Tyrosine 385, which forms a transient radical during the cyclooxygenase reaction, is in purple. Arg 120, which forms an ion pair with fluriprofen, is in green.

from Michael Garavito (see web site)

Figure 14

COX Structure



Ser 530 and Ser 516 are targets of acetylation

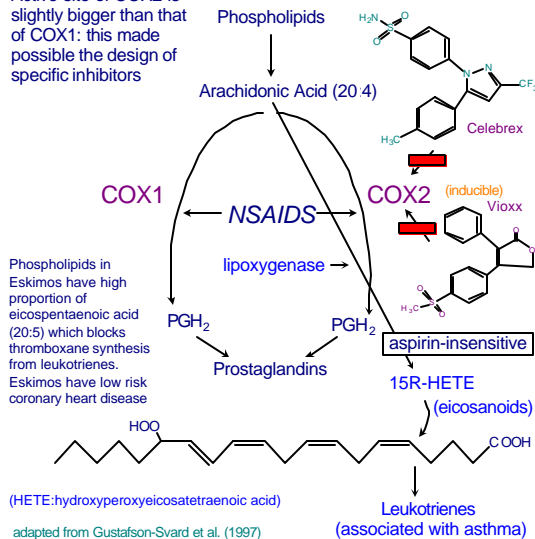
COX3 (target of acetaminophen?)

adapted from Williams and DuBois (1996)

Figure 15

Two Isoforms of PGH₂ Synthase: COX1 and COX2

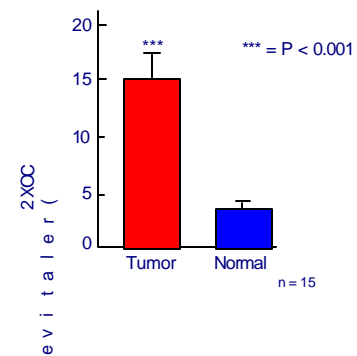
Active site of COX2 is slightly bigger than that of COX1: this made possible the design of specific inhibitors



adapted from Gustafson-Svard et al. (1997)

Figure 16

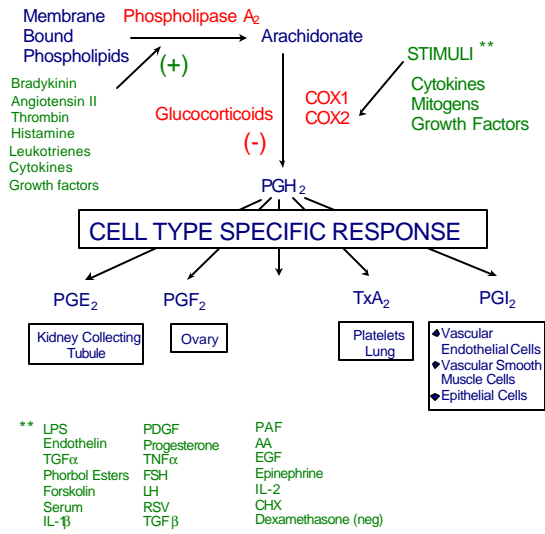
COX2 mRNA Content in Human Colon Tumors



adapted from Gustafson-Svard et al. (1997)

Figure 17

Overview of Arachidonic Acid Metabolism



adapted from Williams and DuBois (1996)