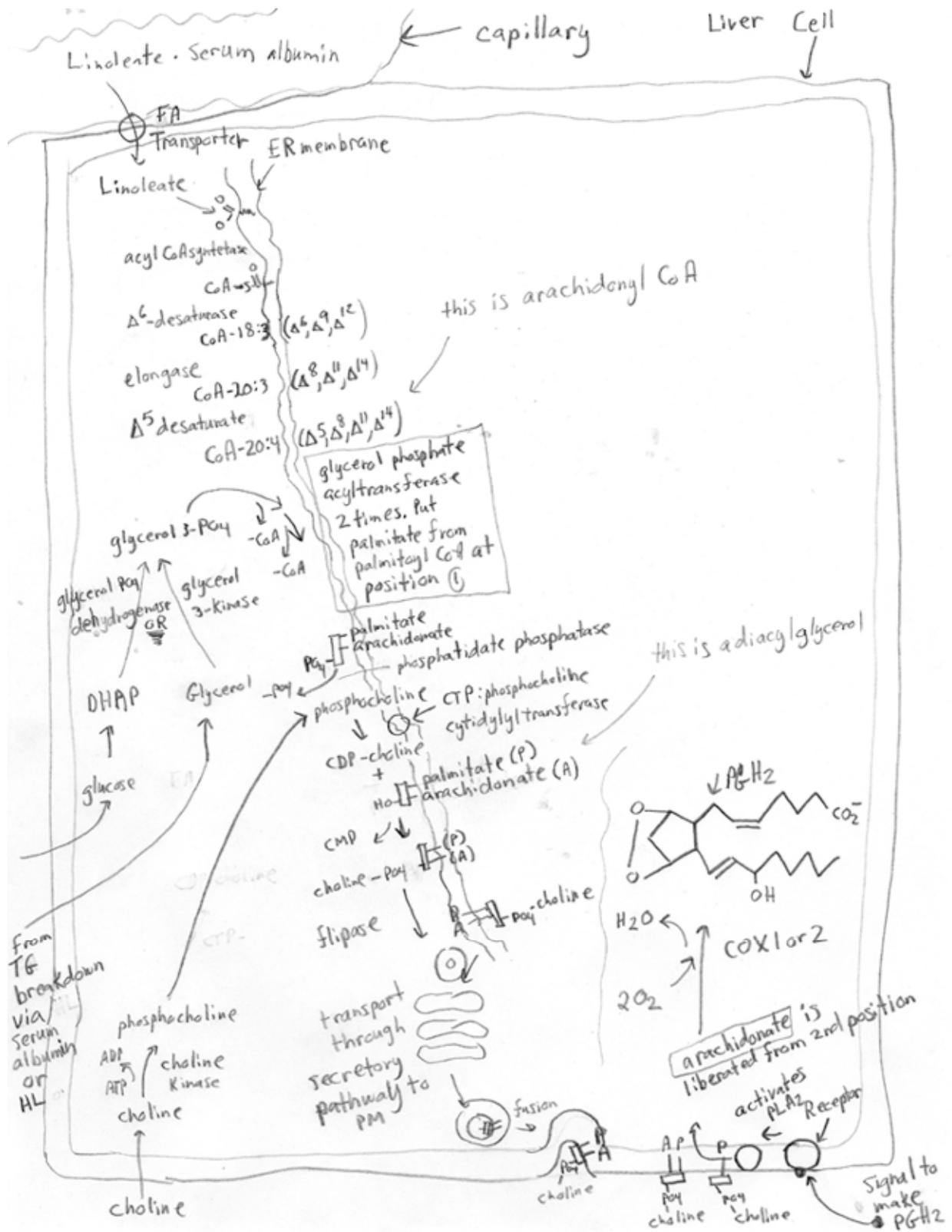


Eicosanoid Synthesis--12. Nov. 2002

1) Start with dietary linoleate (linoleic acid, this was mislabeled as linolenate in the study question) and draw the pathway to make PGH₂.



2) What are COX inhibitors and how do they work?

COX inhibitors are inhibitors of cyclooxygenase, the key rate-limiting enzyme in the synthesis of prostaglandins and thromboxanes, but not leukotrienes.

There are 2 isozymes of COX called COX-1 and COX-2. COX-1 is used to synthesize prostaglandins that ensure mucin secretion to protect the lining of the stomach among other things. COX-2 is the inducible isozymes whose overproduction results in producing inflammatory prostaglandins linked to osteoarthritis among other things. (There is also a recently discovered COX-3 in the brain that was not discussed in lecture that may be the target of acetaminophen.)

COX inhibitors can be selective for COX-2 or non-selective. Non-selective inhibitors include aspirin, that acetylates an active site serine and irreversibly inhibits both COX isozymes and ibuprofen that is a competitive inhibitor of both COX isozymes.

COX-2 selective inhibitors include Celecoxib and Rofecoxib and they significantly inhibit COX-2 more than COX-1 and have fewer gastrointestinal side effects.

3) What is the biochemical basis for aspirin-sensitive asthma?

Aspirin-sensitive asthma results from inhibiting COX enzymes resulting in arachidonate to be excessively synthesized into leukotrienes that are potent vasoconstrictors. Leukotrienes are synthesized from arachidonate, but use the 5-lipoxygenase or 12-lipoxygenase enzymes rather than COX in their key first step of biosynthesis. Aspirin does not inhibit lipoxygenases. In some individuals the amount of leukotrienes synthesized in the bronchiole smooth muscle is sufficient to cause an asthma attack after taking a COX inhibitor like aspirin, ibuprofen, etc.