Eicosanoids are specialized signaling molecules primarily derived from arachidonate (from linoleate).

Eicosanoids are short-lived local signalling molecules

Eicosanoids are divided into 4 classes: Prostaglandins, Prostacyclins, Leukotrienes, Thromboxanes
They are derived from Arachidonic acid through two main pathways: 
cox pathway, lipoxygenase pathway

Prostaglandins: 5 point ring
Thromboxanes: 6 point ring with O
Prostacyclins: double ring
Leukotrienes: absent ring, ≥3 dbl bonds
Eicosanoids typically interact with specific G-protein coupled receptors

1. Hormone binds to a specific receptor.
2. Occupied receptor interacts with G protein.
3. G protein releases GDP and binds GTP.
4. The active subunit of G protein desensitizes and activates phospholipase C.
5. Phospholipase C cleaves phosphatidylinositol 4,5-bisphosphate to inositol triphosphate (IP3) and diacylglycerol (DAG).
6. IP3 binds to a specific receptor on the endoplasmic reticulum, causing release of sequestered Ca2+.
7. Calcium and DAG activate protein kinase C.
8. Protein kinase C catalyzes phosphorylation of cellular proteins that mediate cellular response to the hormone.

Linoleic acid and Arachidonate are essential fatty acids

Some arachidonate can be derived from linoleic acid in the ER

Arachidonate is incorporated into phospholipids

phosphatidylinositol
Phospholipase C cleaves phosphatidylinositol to release DAG

Cytoplasmic phospholipase A2 cleaves arachidonate from phosphatidyl inositol in the outer ER membrane

Ca\(^{2+}\) binding drives membrane association of phospholipase A2

COX isoforms homodimerize

membrane-binding catalytic epidermal growth factor

COX isoforms catalyze committed step in prostaglandin, prostacyclin, and thromboxane synthesis

- Both COX1 and COX2 synthesize PGH: it is not clear how or why they function differently downstream
- COX1 homodimer (constitutive) mediates gastric function, renal homeostasis, and platelet aggregation
- COX2 homodimer (inducible) mediates pain, swelling, inflammation and fever.
COX peroxidase activity

A heme prosthetic group generates the tyrosyl radical

COX cyclooxygenase activity

The redox active tyrosine (tyrosyl radical) mediates cyclooxygenation
Figure 7 A schematic of the COX reaction as proposed by Malkowski et al. (38). While the formation of the 11-peroxy-arachidonate intermediate is explained by the crystal structure for the ovine COX-1/AA complex, its subsequent conversion to PGG₂ requires a major conformational transition that has not been observed or characterized. While the formation of PGG₂ is now fairly well explained, why 11R-HPETE, 15R-HPETE, and 15S-HPETE are formed is unclear. Thuresson et al. (86) presented biochemical evidence that each COX product may arise from a different but catalytically competent conformer of AA. In essence, hydrogen abstraction can occur when AA is not in a conformation that allows facile ring closure, which then leads to the monooxygenation of the substrate. This may mean that the observed structure of AA bound in the COX-1 active site (38) may be a time- and space-average of more than one AA conformer, of which only the predominant conformer...
Aspirin is an irreversible inhibitor of both COX-1 and COX-2

- Ibuprofen and naproxen are competitive inhibitors of both COX-1 and (7-fold) COX-2
- Vioxx and Celebrex are highly selective for COX-2 (300-fold)
patients with connective tissue diseases who had multiple risk factors for hypercoagulability (Crofford et al., 2000), implying an increased thrombogenic risk for specific COX-2 inhibitors in certain patient populations. However, hitherto published clinical studies have yielded discrepant results in this regard. In the CLASS trial, no difference was noted in the incidence of cardiovascular events (cerebrovascular accident, myocardial infarction, angina) between celecoxib and NSAIDs (ibuprofen, diclofenac) (Silverstein et al., 2000). On the other hand, in the VIGOR study, patients receiving rofecoxib had a significant 4-fold increase in the incidence of myocardial infarctions, compared with patients randomized to naproxen (Bombardier et al., 2000). However, as both compounds are known to cause a similar inhibition of systemic prostacyclin production without altering platelet-derived thromboxane synthesis, the apparent discrepancy of these studies in terms of cardiovascular outcome is most likely due to differences in the study protocols (e.g., eligibility criteria, study population, study duration) and the use of different NSAID comparators (Fitzgerald et al., 2000). Accordingly, 22% of the patients included in the CLASS trial took aspirin as a cardioprotective agent, whereas the entry criteria for the VIGOR study precluded aspirin consumption. In addition, the VIGOR study was performed on patients with rheumatoid arthritis, a condition that has been associated with an enhanced rate of cardiovascular events. By contrast, in the CLASS trial patients with osteoarthritis were included that have not been associated with an increased risk of cardiovascular complications. As a consequence, a possible thrombogenicity of specific COX-2 inhibitors deserves further well controlled studies.

COX-2 and Reproductive Functions

COX-2-deficient mice fail to ovulate and have abnormal implantation and decidualization responses (for review, see Langenbach et al., 1999). A recently published study (Davis et al., 1999) has now provided evidence that COX-2 induced by luteinizing hormone in preovulatory follicles is essential for the stabilization of the cumulus oophorum during ovulation. Moreover, COX-2 has been shown to play a role in pregnancy. Expression of COX-2 has been observed in the uterine epithelium at different times during early pregnancy (Chakraborty et al., 1996). Here, COX-2 may be involved in the implantation of the ovum, in the angiogenesis needed for the establishment of the placenta, and in the induction of labor (Gibb and Sun, 1996). It has recently become clear that up-regulation of COX-2 expression mediates increased prostaglandin synthesis in the human myometrium (Slater et al., 1999a) and within the fetal membrane (Slater et al., 1999b) at term. In a subsequent study (Sawdy et al., 2000), specific COX-2 inhibitors were shown to be as effective as non-selective NSAIDs in inhibiting fetal membrane prostaglandin synthesis, suggesting that these drugs may also represent a new strategy for the treatment of tocolysis. However, COX-2 has also revealed as the more essential isoform for initiation of ductus arteriosus closure, suggesting that maternal use of COX-2-specific inhibitors near the time of delivery has the potential to increase the incidence of patent ductus arteriosus after birth (Loftin et al., 2001).

The question whether COX-2 plays a role in renal development was recently addressed by Komhoff et al. (2000) who demonstrated that administration of a specific COX-2 inhibitor in rats and mice during pregnancy until weaning significantly reduced renal function. In a subsequent study (Sawdy et al., 2000), specific COX-2 inhibitors were shown to be as effective as non-selective NSAIDs in inhibiting fetal membrane prostaglandin synthesis, suggesting that these drugs may also represent a new strategy for the treatment of tocolysis. However, COX-2 has also revealed as the more essential isoform for initiation of ductus arteriosus closure, suggesting that maternal use of COX-2-specific inhibitors near the time of delivery has the potential to increase the incidence of patent ductus arteriosus after birth (Loftin et al., 2001).

COX-2 inhibitors suppress prostacyclin synthesis without a concomitant suppression of thromboxanes
They are derived from Arachidonic acid through two main pathways: COX pathway, lipoxygenase pathway.