OBJECTIVES

After studying the material of this lecture, the student will:

1. Draw the structure of a prostaglandin, name the fatty acid from which it is biosynthesized and discuss the manner in which nomenclature is assigned.
2. Recognize the structures of different broad classifications of prostaglandins and related substances.
3. Discuss the range of biological activities displayed by these compounds.
4. Describe in broad generalities the pathways leading to synthesis of these compounds.
5. Discuss the pharmacological/physiological effects of aspirin, indomethacin, glucocorticoids, and ω-3 fatty acids in terms of their effects on prostaglandin synthesis.

RESOURCES

Lehninger, Chapter 21

1. STRUCTURES AND NOMENCLATURE OF PROSTAGLANDINS AND OTHER EICOSENOIDS:

   A. Prostaglandins are biologically active 20 carbon fatty acids characterized by a cyclopentane ring formed by a carbon-carbon bond between carbons 8 and 9. They are variously substituted by double bonds, keto, hydroxyl, endoperoxy or hydroperoxy groups, which determine their respective biological activities (see Figure 1).

      1. Systematic nomenclature is based on the structure of prostanoic acid.
      2. Short-hand nomenclature is based on the order in which prostaglandins were isolated and characterized and the number of double bonds in the side chains.

   \[ \text{PGX}_N, \text{where } X = \text{a specific pattern of oxygen substitution or unsaturation and } N = \text{number of double bonds in side chains} \]
3. Minor structural differences dictate major and even paradoxical differences in biological activities such as smooth muscle contraction, inflammation, pain perception and platelet activation; e.g., PGI$_2$ is antiinflammatory and inactivates platelets.

4. Prostaglandins bind to multiple specific membrane receptors to mediate a multitude of physiological and pharmacologic activities, which are structure-dependent, dose-dependent and time-dependent.
B. Thromboxanes are similar to prostaglandins in structure and nomenclature, differing primarily in the presence of an oxane ring rather than a cyclopentane ring (see Figure 2). Their nomenclatures are also quite similar (TXXₙ). However, they have very different biological activities. TXB₂ mediates inflammation and is a potent platelet activator.

Figure 2: Structure of Thromboxane B₂, with PGE₂, for comparison.

C. Leukotrienes have no ring but are similarly substituted with oxygen in their side chain. Their nomenclature is also based on the pattern of substitution and the number of double bonds (LTXₙ). Leukotrienes mediate the inflammatory effects of leukocytes.
II. BIOLOGICAL EFFECTS

A. Various effects of PGE₁ (for example)
   1. smooth muscle contraction
   2. lowers arterial blood pressure
   3. inhibits gastric acid secretion
   4. inhibits platelet aggregation
   5. raises or lowers cAMP levels in different tissues
   6. induces vascular leakage
   7. produces fever
   8. dilates bronchi
   9. stimulates pancreatic secretion
   10. blocks Na⁺/H₂O resorption in GI tract
   11. counteracts vasopressin in kidney
   12. inhibits lipolysis
   13. stimulates bone resorption
   14. induces vasodilation in many tissues

B. Apparent paradoxical effects
   1. different effects by different compounds in same organ (TXA₂ stimulates; PGI₂ inhibits platelet aggregation.)
   2. different effect by same compound in different parts of same organ
   3. different effect by same compound under different conditions
   4. opposite effects in different species
   5. opposite effect with different concentrations
6. opposite effect with different compound of same family (one double bond different)

III. BIOSYNTHESIS OF PROSTAGLANDINS AND THROMBOXANES BEGINS WITH CYCLOOXYGENASE (see Figure 4):

A. Two reactions of membrane-bound cyclooxygenases:

1. Formation of the 9,11-endoperoxide/15-hydroperoxide, (PGG₉) from a 20 carbon polyunsaturated precursor (e.g., arachidonate).
2. Hydroperoxidase activity to produce PGH₉, the precursor of other prostaglandins and thromboxanes.

![Figure 4: The cyclooxygenase and hydroperoxidase reactions of prostaglandin synthetase.]

B. Other prostaglandins and thromboxanes are produced from PGH by specific synthases (e.g., thromboxane B synthase).

C. Classes of cyclooxygenase:

1. COX-1 (constitutive; produces prostaglandins important to maintenance of gastric mucosa)
2. COX-2 (induced by inflammation; coupled to production of inflammatory prostaglandins, thromboxanes)
3. COX-3?

D. Aspirin and other non-steroidal antiinflammatory drugs inhibit prostaglandin synthesis by binding to the active site of COX.
1. Aspirin acetylates the active site and irreversibly inhibits all classes.
2. A new class of COX-2 inhibitors is specific for COX-2, specifically inhibiting production of inflammatory/pain producing prostaglandins/thromboxane while permitting synthesis of beneficial species in stomach mucosa. Recent studies suggest increased risk of heart attack/stroke.

E. Different fatty acids give rise to different prostaglandins with different biological activities (see Figure 5). The number of double bonds in the product is determined by the number in the precursor fatty acid.

![Figure 5: Different fatty acids give rise to different prostaglandins with different biological activities.](image)

IV. SYNTHESIS (see Figure 6):

A. As discussed earlier, COX-2 can be induced at the transcriptional level by inflammation. This is a long-term mode of regulation, which can influence the mix of eicosanoids.
Figure 6: Pathways for biosynthesis of prostaglandins and leukotrienes, showing the role of phospholipase in regulation of fatty acid availability and sites of action of antiinflammatory drugs. Whereas antiinflammatory steroids block synthesis of all eicosanoid metabolites, the NSAIDS are more selective. Some are targeted to specific cyclooxygenases (COX-1, COX-2, COX-3).

B. In the short term, synthesis of eicosanoids (prostaglandins, thromboxanes, leukotrienes and other inflammatory hydroxy acids) is regulated by membrane phospholipase A2 activity, which releases precursor fatty acids (eicosatrienoic, arachidonic and eicosapentaenoic) from membrane phosphoglycerides.

1. PLA2 can be activated by specific hormones, signaling pathways or nerve stimulation, or by less specific events such as inflammation or trauma.
2. PLA$_2$ activity is substantially regulated by inhibitory proteins, which are induced by steroids. This is a mechanism of action for steroidal inflammatory agents such as cortisone.

3. Since inhibition of PLA$_2$ blocks production of all eicosanoids, steroids are generally more effective antiinflammatory agents than COX inhibitors (NSAIDS), which do not block lipoxygenase or monoxygenase pathways.

V. SOME EXAMPLES OF CLINICAL RELEVANCE:

A. The role of aspirin in prevention of myocardial infarction (see Figure 7): Based on the observation that platelets preferentially produce the inflammatory thromboxanes, which activate platelets to produce inflammatory cytokines and stick together, while endothelial cells produce the antiinflammatory prostacyclins, which inhibit platelet activity. Aspirin irreversibly inhibits the cyclooxygenases in both cell types but the anuclear platelets are unable to produce new cyclooxygenase.

B. How dietary eicosapentaenoic acid reduces the risk of atherosclerosis and MI (see Figure 8): Remember that the fatty acid precursor dictates the class of prostaglandin/thromboxane produced. TXA$_3$ produced by platelets from EPA does not activate platelets. PGI$_3$ produced by endothelial cells from EPA does inhibit platelets.
VI. SOME SIGNALING PATHWAYS THAT PRODUCE BIOLOGICALLY ACTIVE LIPIDS:

How Eicosapentenoic Acid Reduces Risk of Atherosclerosis and MI

![Diagram](image)

- TXA₃ (doesn't activate platelets)
- PGI₂ (inhibits platelets)

Net effect is to inhibit platelets.
Figure 9: Role of phospholipase A₂ in biosynthesis of biologically active eicosanoids.
Figure 10: Phospholipase C releases diacylglycerol and inositol-tris-phosphate second messengers.