Metabolism of the Eicosanoids

The eicosanoids, which include the prostaglandins (PG), thromboxanes (TX), and leukotrienes (LT), are among the most potent regulators of cellular function in nature and are produced by almost every cell in the body. They act mainly as “local” hormones, affecting the cells that produce them or neighboring cells of a different type.

Eicosanoids participate in many processes in the body, particularly the inflammatory response that occurs after infection or injury. The inflammatory response is the sum of the body’s efforts to destroy invading organisms and to repair damage. It includes the control of bleeding through the formation of blood clots. In the process of protecting the body from a variety of insults, the inflammatory response can produce symptoms such as pain, swelling, and fever. An exaggerated or inappropriate expression of the normal inflammatory response may occur in individuals who have allergic or hypersensitivity reactions.

In addition to participating in the inflammatory response, eicosanoids also regulate smooth muscle contraction (particularly in the intestine and uterus). They increase water and sodium excretion by the kidney and are involved in regulating blood pressure. They frequently serve as modulators; some eicosanoids stimulate and others inhibit the same process. For example, some serve as constrictors and others as dilators of blood vessels. They are also involved in regulating bronchoconstriction and bronchodilation.

Eicosanoids are derived from polyunsaturated fatty acids containing 20 carbon atoms, which are found in cell membranes esterified to membrane phospholipids. Arachidonic acid, derived from the diet or synthesized from linoleate, is the compound from which most of the eicosanoids are produced in the body. Compounds that serve as signals for eicosanoid production bind to cell membrane receptors and activate phospholipases that cleave the polyunsaturated fatty acids from cell membrane phospholipids (Fig. 35.1).

Arachidonic acid is enzymatically metabolized by three major pathways. The two pathways that have been most thoroughly studied are the cyclooxygenase pathway (which produces prostaglandins and thromboxanes) and the lipoxygenase pathway (which produces leukotrienes). The cytochrome P450 pathway generates eicosanoids with less well-defined physiologic functions. Isoprostanes are a relatively new class of eicosanoids derived from nonenzymatic free radical–catalyzed reactions. The isoprostanes are similar to prostaglandins in structure and may play a role in inflammatory responses and free radical–mediated tissue injury. In brain tissue, arachidonic acid can be coupled to ethanolamine to generate anandamide. This compound can bind and activate cannabinoid receptors with actions similar to those of ∆⁹-tetrahydrocannabinol (THC).

Many eicosanoids have very short half-lives, in the range of a few minutes or less. They are rapidly inactivated and excreted.
Since her admission to the hospital for an acute myocardial infarction, Ann Jeina has been taking the bile salt sequestrant cholestyramine and the HMG-CoA reductase inhibitor pravastatin to lower her blood cholesterol levels (see Chapter 34). She also takes 160 mg acetylsalicylic acid (ASA; aspirin) each day. At her most recent visit to her cardiologist, she asked whether she should
continue to take aspirin because she no longer has any chest pain. She was told that the use of aspirin in her case was not to alleviate pain but to reduce the risk of a second heart attack and that she should continue to take this drug for the remainder of her life unless a complication, such as gastrointestinal bleeding, occurred as a result of its use.

Emma Wheezer has done well with regard to her respiratory function since her earlier hospitalization for an acute asthmatic attack. She has been maintained on two puffs of triamcinolone acetonide, a potent inhaled corticosteroid, three times per day, and has not required systemic steroids for months. The glucose intolerance precipitated by high intravenous and oral doses of the synthetic glucocorticoid dexamethasone during her earlier hospitalization resolved after this drug was discontinued. She has come to her doctor now because she is concerned that the low-grade fever and cough she has developed over the last 36 hours may trigger another acute asthma attack.

I. SOURCE OF THE EICOSANOIDS

The most abundant and therefore the most common precursor of the eicosanoids is arachidonic acid (eicosatetraenoic acid, \( \omega_6,20:4,\Delta^5,8,11,14 \)), a polyunsaturated fatty acid with 20 carbons and 4 double bonds (see Fig. 35.1). It is esterified to phospholipids located in the lipid bilayer that constitutes the plasma membrane of the cell. Because arachidonic acid cannot be synthesized de novo in the body, the diet must contain arachidonic acid or other fatty acids from which arachidonic acid can be produced. The major dietary precursor for arachidonic acid synthesis is the essential fatty acid linoleate, which is present in plant oils (see Chapter 33).

The arachidonic acid present in membrane phospholipids is released from the lipid bilayer as a consequence of the activation of membrane-bound phospholipase A2 or C (see Fig. 33.31 and Fig. 35.2). This activation occurs when a variety of stimuli (agonists), such as histamine and the cytokines, interact with a specific plasma membrane receptor on the target cell surface. Phospholipase A2 is specific for the sn-2 position of phosphoacylglycerols, the site of attachment of arachidonic acid to the glycerol moiety. Phospholipase C hydrolyzes phosphorylated inositol

![Fig. 35.2. Release of arachidonic acid from membrane lipids. The binding of a stimulus to its receptor activates pathway 1 or 2.](image-url)
Inflammation involving the mucosal and smooth muscle layers of the respiratory tract plays a major role in the development of acute asthmatic bronchospasm in patients such as Emma Wheezer. Dexamethasone and other potent glucocorticoids are capable of preventing or suppressing this inflammation. In part, the glucocorticoids act by inhibiting the recruitment of leukocytes and monocytes–macrophages into affected areas. They also limit the ability of these cells to elaborate a variety of chemotactic factors and other substances, such as certain eicosanoids, which enhance the inflammatory process. Glucocorticoids, for example, suppress the transcription and translation of the inducible form of the cyclooxygenase enzyme, COX-2. Glucocorticoids also induce the synthesis of a protein or family of proteins (lipocortins or macrocortins) that inhibit the activity of phospholipase A2. As a result, the synthesis of prostaglandins and leukotrienes is decreased, and the inflammatory response in bronchial tissues is reduced (see Figs. 35.1 and 35.2).

from the inositol glycerophospholipids, generating a diacylglycerol containing arachidonic acid. This arachidonic acid is subsequently released by the action of other lipases.

II. PATHWAYS FOR EICOSANOID SYNTHESIS

After arachidonic acid is released into the cytosol, it is converted to eicosanoids by a variety of enzymes with activities that vary among tissues. This variation explains why some cells, such as those in the vascular endothelium, synthesize prostaglandins E2 and I2 (PGE2 and PGI2) whereas cells, such as platelets, synthesize primarily thromboxane A2 (TXA2) and 12-hydroxyeicosatetraenoic acid (12-HETE).

Three major pathways for the metabolism of arachidonic acid occur in various tissues (Fig. 35.3). The first of these, the cyclooxygenase pathway, leads to the synthesis of prostaglandins and thromboxanes. The second, the lipoxygenase pathway, yields the leukotrienes, HETEs, and lipoxins. The third pathway, catalyzed by the cytochrome P450 system, is responsible for the synthesis of the epoxides, HETEs, and diHETEs.

A. Cyclooxygenase Pathway: Synthesis of the Prostaglandins and Thromboxanes

1. STRUCTURES OF THE PROSTAGLANDINS

Prostaglandins are fatty acids containing 20 carbon atoms, including an internal 5-carbon ring. In addition to this ring, each of the biologically active prostaglandins has a hydroxyl group at carbon 15, a double bond between carbons 13 and 14, and various substituents on the ring (Fig. 35.4).

The nomenclature for the prostaglandins (PGs) involves the assignment of a capital letter (PGE), an Arabic numeral subscript (PGE1), and, for the PGF family, a Greek letter subscript (e.g., PGF2α). The capital letter, in this case “F,” refers to the ring substituents shown in figure 35.5.

The subscript that follows the capital letter (PGF1) refers to the PG series 1, 2, or 3, determined by the number of unsaturated bonds present in the linear portion of the hydrocarbon chain (Fig. 35.6). It does not include double bonds in the internal ring. Prostaglandins of the 1-series have one double bond (between carbons 13 and 14). The 2-series has two double bonds (between carbons 13 and 14, and 5 and 6), and the 3-series has three double bonds (between carbons 13, 14, 5 and 6, and 17 and 18). The double bonds between carbons 13 and 14 are trans; the others are cis.

The Greek letter subscript, found only in the F series, refers to the position of the hydroxyl group at carbon 9. This hydroxyl group primarily exists in the α position, where it lies below the plane of the ring, as does the hydroxyl group at carbon 11 (see Figs. 35.4 and 35.5).
Fig. 35.5. Ring substituents of the prostaglandins (PG). The letter after PG denotes the configuration of the ring and its substituents. R₄, R₇, and R₈ represent the non-ring portions of the molecule. R₄ contains four carbons (including the carboxyl group). R₇ and R₈ contain seven and eight carbons, respectively, and correspond to the 1-, 2-, or 3-series shown in Figure 35.6. Note that the prostacyclins (PGI) contain two rings.

2. STRUCTURE OF THE THROMBOXANES

The thromboxanes were named for their action in producing blood clots (thrombi).

The thromboxanes, derived from arachidonic acid via the cyclooxygenase pathway, closely resemble the prostaglandins in structure except that they contain a 6-membered ring that includes an oxygen atom (Fig. 35.7). The most common thromboxane, TXA₂, contains an additional oxygen atom attached both to carbon 9 and carbon 11 of the ring.
3. BIOSYNTHESIS OF THE PROSTAGLANDINS AND THROMBOXANES

Only the biosynthesis of those prostaglandins derived from arachidonic acid (e.g., the 2-series, such as PGE\(_2\), PGI\(_2\), TXA\(_2\)) are described, because those derived from eicosatrienoic acid (the 1-series) or from eicosapentaenoic acid (the 3-series) are present in very small amounts in humans on a normal diet (see Fig. 35.6).

The biochemical reactions that lead to the synthesis of prostaglandins and thromboxanes are illustrated in figure 35.8. The initial step, which is catalyzed by a cyclooxygenase, forms the five-membered ring and adds four atoms of oxygen (two between carbons 9 and 11, and two at carbon 15) to form the unstable endoperoxide, PGG\(_2\). The hydroperoxy group at carbon 15 is quickly reduced to a hydroxyl group by a peroxidase to form another endoperoxide, PGH\(_2\).

The next step is tissue specific (see Fig. 35.8). Depending on the type of cell involved, PGH\(_2\) may be reduced to PGE\(_2\) or PGD\(_2\) by specific isomerases (PGE synthase and PGD synthase). PGE\(_2\) may be further reduced by PGE 9-ketoreductase to form PGF\(_{2\alpha}\). PGF\(_{2\alpha}\) also may be formed directly from PGH\(_2\) by the action of an endoperoxide reductase. Some of the major functions of the prostaglandins are listed in Table 35.1.

PGH\(_2\) may be converted to the thromboxane TXA\(_2\), a reaction catalyzed by TXA synthase (see Fig. 35.8). This enzyme is present in high concentration in platelets. In the vascular endothelium, however, PGH\(_2\) is converted to the prostaglandin PGI\(_2\).

Fig. 35.7. The thromboxane ring. In contrast to the prostaglandins, which have a five-membered carbon ring, thromboxanes have a six-membered ring (shown in blue) containing an oxygen atom. Substituents are attached to the ring at carbons 9 and 11. In the case of TXA\(_2\) (shown above), an oxygen atom connects carbons 9 and 11.

Fig. 35.8. Formation of prostaglandins (including the prostacyclin PGI\(_2\)) and thromboxane TXA\(_2\) from arachidonic acid. The conversion of arachidonic acid to PGH\(_2\) is catalyzed by a membrane-bound enzyme, prostaglandin endoperoxide synthase, which has cyclooxygenase and peroxidase activities. The reducing agent is glutathione (GSH), which is oxidized to GSSG.
The predominant eicosanoid in platelets is TXA₂, a potent vasoconstrictor and a stimulator of platelet aggregation. The latter action initiates thrombus formation at sites of vascular injury as well as in the vicinity of a ruptured atherosclerotic plaque in the lumen of vessels such as the coronary arteries. Such thrombi may cause sudden total occlusion of the vascular lumen, causing acute ischemic damage to tissues distal to the block (i.e., acute myocardial infarction).

Aspirin, by covalently acetylating the active site of cyclooxygenase, blocks the production of TXA₂ from its major precursor, arachidonic acid. By causing this mild hemostatic defect, low-dose aspirin has been shown to be effective in prevention of acute myocardial infarction (see Clinical Comments). For Ivan Applebod (who has symptoms of coronary heart disease), aspirin is used to prevent a first heart attack (primary prevention). For Ann Jeina and Cora Nari (who already have had heart attacks), aspirin is used to prevent a second heart attack (secondary prevention).

Dietary intake of polyunsaturated fatty acids, such as found in cold water fish (e.g., salmon, mackerel, brook trout, herring), results in more TXA₃ relative to TXA₂. TXA₃ is less effective in stimulating platelet aggregation than its counterpart in the 2-series, TXA₂.

Table 35.1. Some Functions of the Prostaglandins

<table>
<thead>
<tr>
<th>Prostaglandins</th>
<th>Increases</th>
<th>Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGI₂, PGE₂, PGD₂</td>
<td>Vasodilation</td>
<td>Platelet aggregation</td>
</tr>
<tr>
<td></td>
<td>cAMP</td>
<td>Leukocyte aggregation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IL-1 and IL-2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T-cell proliferation</td>
</tr>
<tr>
<td>PGF₂α</td>
<td>Increases</td>
<td>Lymphocyte migration</td>
</tr>
</tbody>
</table>

* IL = interleukin, a cytokine that augments the activity of many cells in the immune system.

In the 1990s, the cyclooxygenase enzyme was found to exist as two distinct isoforms, designated COX-1 and COX-2. COX-1 is regarded as a constitutive form of the enzyme, widely expressed in almost all tissues, and involved in the production of prostaglandins and thromboxanes for “normal” physiologic functions. COX-2 is an inducible form of the enzyme regulated by a variety of cytokines and growth factors. COX-2 mRNA and protein levels are usually low in most healthy tissue, but are expressed at high levels in inflamed tissue.

Because of the importance of prostaglandins in mediating the inflammatory response, drugs that block prostaglandin production should provide relief from pain. The cyclooxygenase enzyme is inhibited by all nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin (acetylsalicylic acid). Aspirin transfers an acetyl group to the enzyme, irreversibly inactivating it (Fig. 35.9). Other NSAIDs (e.g., acetaminophen, ibuprofen) act as reversible inhibitors of cyclooxygenase. Acetaminophen is the major ingredient in Tylenol, and ibuprofen is the major ingredient in other NSAIDs such as Motrin, Nuprin, and Advil (see Fig. 35.9). Although having some relative selectivity for inhibiting either COX-1 or COX-2,
NSAIDs block the activity of both isoforms. These findings have provided the impetus for the development of selective COX-2 inhibitors, which are proposed to act as potent anti-inflammatory agents by inhibiting COX-2 activity, without the gastrointestinal and anti-platelet side effects commonly associated with NSAID use. These NSAID adverse effects are thought to be a result of COX-1 inhibition. Examples of these newer selective COX-2 inhibitors are celecoxib (Celebrex) and rofecoxib (Vioxx).

4. **INACTIVATION OF THE PROSTAGLANDINS AND THROMBOXANES**

Prostaglandins and thromboxanes are rapidly inactivated. Their half-lives ($t_{1/2}$) range from seconds to minutes. The prostaglandins are inactivated by oxidation of the 15-hydroxy group, critical for their activity, to a ketone. The double bond at carbon 13 is reduced. Subsequently, both $\beta$- and $\omega$-oxidation of the non-ring portions occur, producing dicarboxylic acids that are excreted in the urine. Active TXA$_2$ is rapidly metabolized to TXB$_2$ by cleavage of the oxygen bridge between carbons 9 and 11 to form two hydroxyl groups. TXB$_2$ has no biologic activity.

**B. Lipoxygenase Pathway: Synthesis of the Leukotrienes, HETE, and Lipoxins**

In addition to serving as a substrate for the cyclooxygenase pathway, arachidonic acid also acts as a substrate for the lipoxygenase pathway. The lipoxygenase enzymes catalyze the incorporation of an oxygen molecule onto a carbon of one of several double bonds of arachidonic acid, forming a hydroperoxy (–OOH) group at these positions. With this oxygenation, the double bond isomerizes to a position one carbon removed from the hydroperoxy group and is transformed from the cis to the trans configuration (Fig. 35.10). The unstable hydroperoxy group is then converted to the more stable hydroxy group.

![Fig. 35.10. Action of lipoxygenases in the formation of HPETEs and HETEs. Lipoxygenases add hydroperoxy groups at position 5, 12, or 15 with rearrangement of the double bond. HPETEs are unstable and are rapidly reduced to form HETEs or converted to leukotrienes and lipoxins (see Figs. 35.11 and 35.12).](image-url)
Lipoxins were so named because they are synthesized in leukocytes and contain the typical triene structure, i.e., three double bonds in series (in this case, at positions 7, 9, and 11) (see Fig. 35.11).

Lipoxygenases may act at carbons 5, 12, or 15. The type of lipoxygenase varies from tissue to tissue. For example, polymorphonuclear leukocytes contain primarily 5-lipoxygenase, platelets are rich in 12-lipoxygenase, and eosinophilic leukocytes contain primarily 15-lipoxygenase.

1. LEUKOTRIENE SYNTHESIS

As shown in figure 35.11, the synthesis of the leukotrienes begins with the formation of hydroperoxyeicosatetraenoic acids (HPETEs). This product is either reduced to the corresponding hydroxy metabolites, HETEs (see Fig. 35.10), or it is metabolized to form leukotrienes or lipoxins (see Figs. 35.11 and 35.12). The major leukotrienes are produced by 5-lipoxygenase.

In leukocytes and mast cells, 5-HPETE is converted to an epoxide, leukotriene A₄ (LTA₄). The subscript number 4 refers to the presence of four double bonds in the leukotriene. Three of the double bonds (7, 9, 11) are conjugated, that is, they form a triene.

Other functional leukotrienes are formed from LTA₄ by one of two pathways. In the first, LTA₄ is converted to LTB₄, a 5,12-dihydroxy derivative. The second metabolic pathway involves the addition of reduced glutathione to carbon 6 to form LTC₄, a reaction catalyzed by glutathione S-transferase. Glutamate is removed from the glutathione moiety of LTC₄ through the action of γ-glutamyl transpeptidase to form LTD₄. A dipeptidase then cleaves the glycine residue from LTD₄ to form LTE₄ (see Fig. 35.11). The major functions of some of the leukotrienes are listed in Table 35.3.

Fig. 35.12. Formation of the lipoxins. These compounds contain three hydroxyl groups.

Fig. 35.11. Formation of leukotrienes and their glutathione (GSH) derivatives. HPETE = hydroperoxyeicosatetraenoic acids; LT = leukotriene (thus, LTA₄ is leukotriene A₄).
2. LIPOXIN SYNTHESIS AND ACTIONS

The lipoxins are formed through the action of 15-lipoxygenase followed by the action of 5-lipoxygenase on arachidonic acid. A series of reductions of the resultant hydroperoxy groups leads to the formation of trihydroxy derivatives of arachidonic acid known as the lipoxins (see Fig. 35.12). Lipoxins induce chemotaxis and stimulate superoxide anion production in leukocytes.

C. Cytochrome P450 Pathway: Synthesis and Actions of Epoxides, HETEs, and diHETES

A third mechanism for the oxygenation of arachidonic acid involves the cytochrome P450 pathway. The activity of the monooxygenases in this microsomal system yields epoxides, certain forms of HETEs (e.g., ω-hydroxy derivatives), and diol forms (diHETEs) (Fig. 35.13). The biologic activities of these compounds include actions in ocular, vascular, endocrine, and renal systems. Some of these actions are attributed to inhibition of Na⁺, K⁺-ATPase. The physiologic role of these compounds remains to be fully characterized.

D. Isoprostane Synthesis

Isoprostanes are derived from arachidonic acid by lipid peroxidation, initiated by free radicals. There is no enzymatic mechanism for their production. Arachidonic acid, while still a component of a phospholipid, undergoes free radical damage, and then phospholipase A2 removes the altered eicosanoid from the phospholipid and releases it into circulation (Fig. 35.14). The level of isoprostanes in the urine can be used as a measure of the oxidative stress of a patient and is a useful biologic marker for patients undergoing oxidative stress caused by a variety of disorders. Surprisingly, these altered arachidonic acid molecules also have biologic activity when measured on cultured cells; it is not known whether intracellular levels reach high enough concentrations to elicit these biologic effects. The best studied isoprostane is similar to PGF₂α, and this molecule has similar effects on cultured cells as does PGF₂α (see Table 35.1).

E. Endocannabinoid Synthesis

Endocannabinoids are endogenous ligands for the cannabinoid receptor, with effects primarily in the nervous system. Anandamide was the first such ligand isolated and identified. Anandamide is synthesized in neurons from phosphatidylethanolamine, as outlined in figure 35.15. The biosynthetic pathway is unique in transferring an arachidonic acid group from the 2-position to the free amino group on ethanolamine, and then using a unique phospholipase D to cleave the modified ethanolamine from the phospholipid. The synthesis of anandamide is regulated, in part, by agonists that cause calcium influx into nerve cells. Once anandamide is released, it acts as a retrograde messenger, binding to receptors on the presynaptic membrane that alter ion fluxes such that neurotransmitter release from the presynaptic neuron can be increased and an analgesic effect obtained. Anandamide is degraded by the enzyme fatty acid amide hydrolase, which splits anandamide to arachidonic acid and ethanolamine. The hydrolase enzyme is the target of drug research, because inhibiting the action of this enzyme will prolong the analgesic effects induced by anandamide.

III. MECHANISM OF ACTION OF THE EICOSANOIDS

The eicosanoids have a wide variety of physiologic effects, which are generally initiated through an interaction of the eicosanoid with a specific receptor on the plasma membrane of a target cell (Table 35.4). This eicosanoid-receptor binding either activates the adenylate cyclase-cAMP-protein kinase A system (PGE, PGD,
Fig. 35.14. Generation of an isoprostane. Radical damage to a phospholipid on the arachidonic acid residue at position 2 generates an isoprostane, which is then removed from the damaged phospholipid by phospholipase A2. The example of an isoprostane shown in this figure is just one of many that can be produced.

Fig. 35.15. Anandamide synthesis and degradation. TAE = transacylase.

<table>
<thead>
<tr>
<th>Table 35.4. Prostaglandin and Thromboxane Receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Receptor</strong></td>
</tr>
<tr>
<td>DP</td>
</tr>
<tr>
<td>EP1</td>
</tr>
<tr>
<td>EP2</td>
</tr>
<tr>
<td>EP3</td>
</tr>
<tr>
<td>EP4</td>
</tr>
<tr>
<td>FP</td>
</tr>
<tr>
<td>IP</td>
</tr>
<tr>
<td>TP</td>
</tr>
</tbody>
</table>
Although our knowledge of the spectrum of biologic actions of the endogenous eicosanoids is incomplete, several actions are well-enough established to allow their application in a variety of clinical situations or diseases. For example, drugs that are analogs of PGE<sub>1</sub> and PGE<sub>2</sub> suppress gastric ulceration, in part by inhibiting secretion of hydrochloric acid in the mucosal cells of the stomach. Analogs of PGE<sub>1</sub> are used in the treatment of sexual impotence. Men with certain forms of sexual impotence can self-inject this agent into the corpus cavernosum of the penis to induce immediate but temporary penile tumescence. The erection lasts for 1 to 3 hours.

Some of the biologic effects of certain eicosanoids occur as a result of a paracrine or autocrine action. One paracrine action is the contraction of vascular smooth muscle cells caused by TXA<sub>2</sub> released from circulating platelets (vasoconstriction). An autocrine action of eicosanoids is exemplified by platelet aggregation induced by TXA<sub>2</sub> produced by the platelets themselves.

The eicosanoids influence the cellular function of almost every tissue of the body. Certain organ systems are affected to a greater degree than others.

**CLINICAL COMMENTS**

In the presence of aspirin, cyclooxygenase is irreversibly inactivated by acetylation. New cyclooxygenase molecules are not produced in platelets, because these cells have no nuclei and, therefore, cannot synthesize new mRNA. Thus, the inhibition of cyclooxygenase by aspirin persists for the lifespan of the platelet (7–10 days). When aspirin is taken daily at doses between 81 and 325 mg, new platelets are affected as they are generated. Higher doses do not improve efficacy but do increase side effects, such as gastrointestinal bleeding and easy bruisingability.

Patients with established or suspected atherosclerotic coronary disease, such as Ann Jeina, Cora Nari, and Ivan Applebod, benefit from the action of low-dose aspirin (approximately 162 mg/day), which produces a mild defect in hemostasis. This action of aspirin helps to prevent thrombus formation in the area of an atherosclerotic plaque at critical sites in the vascular tree.

Corticosteroids reduce inflammation, in part, through their inhibitory effect on phospholipase A<sub>2</sub>. In addition, suppression of COX-2 induction is now thought to be a primary anti-inflammatory mechanism of action for glucocorticoids. Despite the unquestionable value of glucocorticoid therapy in a variety of diseases associated with acute inflammation of tissues, the suppression of the inflammatory response with pharmacologic doses of corticosteroids is potentially hazardous. The sudden appearance of temporary glucose intolerance when Emma Wheezer was treated with large doses of dexamethasone, a gluconeogenic steroid (glucocorticoid), is just one of the many potential adverse effects of this class of drugs when given systemically in pharmacologic doses over an extended period. The inhaled steroids, conversely, have far fewer systemic side effects because their absorption across the bronchial mucosa into the circulation is very limited. This property allows them to be used over prolonged periods in the treatment of asthma. The fact that inhalation allows direct delivery of the agent to the primary site of inflammation adds to their effectiveness in the treatment of these patients.

**BIOCHEMICAL COMMENTS**

Inflammation is the response of the body to infection or injury, directed at destroying the infectious agents and repairing the damaged areas. It involves an increase of the blood supply to the affected region by means of
Although uncomfortable, the pain, swelling, and fever that are part of the inflammatory response serve as an important warning sign that the host is threatened and that some specific counteractions must be taken against the offending agent or process. Although the use of anti-inflammatory drugs may bring welcome symptomatic relief, their use may, in part, diminish the effectiveness of the host’s response to the inciting agent.

Vasodilation. The capillaries become more permeable so that fluid, large molecules, and white blood cells can cross, leaving the blood and entering the tissue. White blood cells (particularly neutrophils and monocytes) move by chemotaxis to the injured site. Redness (rubor), heat (calor), swelling (tumor), and pain (dolor) are associated with the inflammatory process. Redness and heat are caused by the increased blood flow. Swelling is the result of the increased movement of fluid and white blood cells into the area of inflammation. Pain is caused by the release of chemical compounds and the compression of nerves in the vicinity of the inflammatory process.

The chemical mediators of inflammation usually are produced by activation of complement (a family of blood proteins that are cleaved to form active fragments) or of the blood clotting cascade (see Chapter 45). These processes cause the release of histamine from mast cells, and the production of kinins by cleavage of kininogens. Among their other effects, both histamine and kinins increase vascular permeability. They stimulate the synthesis of eicosanoids that act on the motility and metabolism of white blood cells and cause the aggregation of platelets to arrest bleeding. Some of the prostaglandins act on thermoregulatory centers of the brain, producing fever. Cytokines are also released that stimulate the proliferation of cells involved in the immune response.

Suggested References


REVIEW QUESTIONS—CHAPTER 35

1. In humans, prostaglandins are primarily derived from which of the following?
   (A) Glucose
   (B) Acetyl CoA
   (C) Arachidonic acid
   (D) Oleic acid
   (E) Leukotrienes

2. Aspirin will inhibit which of the following reaction pathways?
   (A) Arachidonic acid → thromboxanes
   (B) Arachidonic acid → leukotrienes
   (C) Arachidonic acid → phospholipids
   (D) Linoleic acid → arachidonic acid
   (E) Acetyl CoA → linoleic acid
3. Which of the following drugs leads to the covalent modification, and inactivation, of both the COX-1 and COX-2 enzymes?
   (A) Aspirin
   (B) Tylenol
   (C) Celebrex
   (D) Vioxx
   (E) Advil

4. Thromboxane A₂, which is found in high levels in platelets, aids in wound repair through induction of which of the following activities?
   (A) Inhibits COX-2 gene expression
   (B) Inhibits COX-1 gene expression
   (C) Vasoconstriction
   (D) Vasodilation
   (E) Bronchodilation

5. Certain prostaglandins, when binding to their receptor, induce an increase in intracellular calcium levels. The signal that leads to the elevation of intracellular calcium is initiated by which of the following enzymes?
   (A) Protein kinase A
   (B) Phospholipase C
   (C) Phospholipase A₂
   (D) Protein kinase C
   (E) Cyclooxygenase