Review

Biochemical and nutritional aspects of eicosanoids

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The eicosanoids are derived from 20-carbon polyunsaturated fatty acids e.g., dihomogamma linolenic, arachidonic, eicosapentaenoic, and Mead acid, which are present as components of cell membrane phospholipids. Activation of phospholipases causes release of these fatty acids that can be metabolized either via the cyclooxygenase pathway to produce the prostanoids–prostaglandins, thromboxanes, and prostacyclins—or via the lipoxygenase pathway to form leukotrienes and lipoxins. These fatty acids can also be oxidized by the cytochrome P-450 system giving rise to several metabolites including epoxyeicosatrienoic acids. Eicosanoids are highly active substances with diverse biological actions. Because arachidonic acid is the most common fatty acid present in tissue lipids, the eicosanoids derived from it predominate in human tissues. Some of the eicosanoids formed from arachidonic acid such as thromboxane A_2 and leukotrienes have deleterious effects, while those derived from other polyunsaturated fatty acids are generally less potent or have beneficial actions. The steroidal anti-inflammatory agents, such as cortisone, block the release of precursor fatty acids and thus the formation of all eicosanoids. Non-steroidal anti-inflammatory agents such as aspirin inhibit cyclooxygenase and prevent the production of prostanoids. It is possible to modulate the precursor fatty acid component in cell membrane phospholipids by dietary means, which in turn can alter the types of eicosanoids formed endogenously. Some food constituents such as vitamin C, vitamin E, garlic, onion, ginger, and alcohol can affect the production of eicosanoids. The dietary manipulation may serve as a long-term strategy to favorably modify the endogenous eicosanoid production.

Keywords: prostanoids; leukotrienes; lipoxins; cytochrome P-450 products; dietary modification; vitamin C; vitamin E; garlic

Historical perspective

During 1929–1930 two seemingly unrelated developments began. The work of biochemists George and Mildred Burr at the University of Minnesota led to the discovery of essential fatty acids necessary for normal physiologic functions in animals and humans.[1,2] The other study at about the same time in New York, which had a less clearly defined origin, led to the eventual discovery of prostaglandins and related compounds. We now know that these two discoveries are intimately related.

Two researchers from the Department of Obstetrics and Gynecology at the Columbia University in New York, Kurzrok and Lieb,[3] were working on the problem of infertility in women. While trying artificial insemination they observed one of the two effects after the introduction of small amounts (0.5 mL) of semen in the uterine cavity. In some patients the seminal fluid would be promptly expelled as a result of strong contraction of the uterus while in others it would be retained. They related these findings to women being fertile when the fluid was retained and infertile when the fluid was expelled. They also found that fresh human semen would cause either strong contraction or relaxation in isolated strips of the human uterus. The uterus strips of patients who had successful pregnancies responded to semen in vitro by relaxing, but the strips of patients with a history of infertility gave a contractile response. However, these investigators also noted that the same uterus strips sometimes would respond to one specimen by relaxation and then contraction with another specimen. Therefore, the conclusions related to fertility based on these observations were not correct, but these studies helped gain knowledge of the active principle in seminal fluid. Their findings might now be accounted for by the content of the active principle in the sample, the nature of receptors in the uterine muscle for this active substance, and the probability of intake of drugs such as aspirin by patients.

In 1933 Goldblatt[4] in England and Von Euler[5] in

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Sweden independently reported that lipid fractions of seminal plasma stimulated smooth muscle to contract or, on injection into the experimental animal it sharply lowered blood pressure. Goldblatt worked with specimens from human volunteers, and Von Euler used seminal fluids of monkeys, sheep, and goats and extracts of the vesicular glands of sheep. Because of the assumption that the active substance was made by the prostate gland, Von Euler suggested the name prostaglandin (PG) for this remarkably potent material.[6] Actually the term was a misnomer because the active substance came from the seminal vesicles, glands that also contribute to semen.

For the first 10 years after its discovery, all PG research was done in Von Euler's laboratory. But because of World War II the work in this field was stopped. Early investigators found it very difficult to quantitate the PGs and determine their structures despite their potent biological activity. They are found naturally in minute quantities and are inactivated in a very short period of time. Technology was too primitive to isolate and identify microscopic amounts of unstable molecules. In most tissues and body fluids the amount of PG found is less than 0.5 μg per gram of wet tissue, but human seminal fluid contains more than 100 μg per gram. Were it not for this source we might still be waiting for its discovery.

It was not until 1960 that the first pure PG preparations were isolated by Bergstrom and Sjovall[7,8] in Sweden. They showed in work with others that PG was not a single substance but a mixture of several compounds.[9] One of the problems after the identification of different PGs was that these compounds, isolated from biological sources, were in too small amounts to allow broad biological testing. In 1964 Van Dorp et al.[10] and Bergstrom et al.[11] independently reported that radiolabeled arachidonic acid was incorporated into PGs, and thus a link was established between essential fatty acids and PGs. This led to the large scale biosynthesis of PGs from arachidonic acid using crude enzyme preparations from 4200 kg of seminal vesicles obtained from more than 500,000 sheep. The estimated cost of 1 g of PG was little more than $3,000. The Upjohn Company in the United States and Unilever in The Netherlands financially supported this project and made gram quantities of PGs available to a large number of investigators around the world. In 1969 Weinheimer and Spraggins[12] discovered that PG derivatives could be obtained from a gorgonian coral called *Plexaura homomalla,* or sea whip, collected in the Caribbean Sea. It was then found that relatively pure PG could be extracted in amounts up to 1.5% of the wet weight of the *P. homomalla.* By the end of the 1960's and early 1970's the research on PGs continued at a very rapid pace, and in several directions such as the biosynthesis and metabolism, the potential uses of these novel compounds in various clinical conditions, the synthesis of different PGs and analogs,[13] the effects of aspirin and other nonsteroidal antiinflammatory agents on the biosynthesis of PGs, and the discovery of other related compounds.[14]

In 1969 Piper and Vane[15] described the release of a short-lived substance during anaphylaxis in isolated lungs from sensitized guinea pigs. Because of its activity they called it rabbit aorta contracting substance (RCS). Hamberg et al.[16] then found that a potent aggregating factor resembling the major component of RCS could be generated by the addition of arachidonic acid to human blood platelets. This factor lacked the prostanoic acid backbone of PGs, and it was designated thromboxane because of its formation and probable role in aggregating platelets and the characteristic oxane ring structure.

The discovery of another related compound came in 1976 when Monkada et al.[17] were surveying various biological tissues for the ability to produce thromboxane. They found that hog aorta microsomes produced a new substance that relaxed certain vascular muscle strips and was a potent inhibitor of platelet aggregation. These investigators tentatively named the new substance PGX, and after the identification of its unique bicyclic structure[18] it was renamed prostacyclin.

Eight years after the first observations of PG effects in 1930, another substance having effect on smooth muscle was detected by Feldberg and Kellaway.[19] The new material released from guinea pig lung that was perfused with cobra venom caused the middle small intestinal segment to contract. Because of the slow onset of contraction (slower than that produced by histamine) the material was called slow reacting substance (SRS). Two years later[20] the same (or a similar) substance was detected in related experiments involving well-known allergy producing substances (allergens). In the early 1950s Brocklehurst[21,22] coined the term SRS-A to describe the reactive material generated during anaphylactic events as contrasted to the material released by other means. It is now known that both SRS and SRS-A are essentially the same. As with PGs, the work on the chemical identification of the substance was initially limited because of the lack of pure preparation. It was characterized as a sulfur-containing lipid soluble substance.[23] It was also shown that labeled arachidonic acid was incorporated into SRS.[24,25] The structural work on SRS was performed on material isolated from murine mastocytoma cells, and the complete structure was reported in 1979.[26] It was found that SRS contains a mixture of substances that were named leukotrienes because of their original discovery in leukocytes and the presence of three conjugated double bonds in the molecule.[27] Recently a new family of compounds derived from arachidonic acid and named as lipoxins[28] and metabolites of cytochrome P-450 action on arachidonic acid[29,30] have been described. The physiological importance of these products remains to be clarified.

Prostaglandins

Structure and nomenclature

PGs are 20-carbon carboxylic acids and all have the same basic carbon skeleton of the hypothetical parent

compound prostanoic acid *(Figure 1)*. There are several types of PGs and all the naturally occurring PGs have a five-membered (cyclopentane) ring, two aliphatic chains, and a terminal carboxyl group. All PGs have C_{13}:C_{14} double bond and a 15-hydroxyl group, which appears to be essential for PG biological activity.

The letters E and F are derived from the early observations that PGs could be partially separated by ether extraction of tissue homogenates of phosphate ("fosfat" in Swedish) buffer. Those soluble in ether belong to the E series, whereas F types are those soluble in aqueous phase.[7,8,31] The E series is characterized by the presence of the 11, hydroxy and 9, keto group, and F series has two hydroxyl groups, one at 9 and the other at the 11 position. The subscripts 1, 2, or 3 represent the number of carbon-carbon double bonds present in the side chain emanating from the cyclopentane ring. An alpha/beta system is employed to define the stereochemistry of functions on the cyclopentane ring. Alpha signifies that the substitutions are oriented on the same side of the ring as the aliphatic chain bearing COOH group (e.g., hydroxyl group at C_9 is cis to the COOH side chain), whereas beta substituents are oriented on the side of the ring bearing the alkyl side chain (C_{13} to C_{20}). The PGs with alpha subscript occur naturally and compounds with beta configuration are produced synthetically.

In the E_1 and $F_{1\alpha}$ there is the basic C_{13}:C_{14} double bond, for E_2 and $F_{2\alpha}$ there is an additional double bond at C_5:C_6, and for E_3 and $F_{3\alpha}$ one more double bond is located at C_{17}:C_{18}. The A series is derived from the E series by loss of water from the cyclopentane ring and the B series is derived from A by isomerization of the ring double bond from the C_{10}:C_{11} to C_8:C_{12} position *(Figure 2)*. The D series has a hydroxyl group at C_9 and a keto group at C_{11} (opposite substitution of E series).

Occurrence

PGs are widely distributed in tissues and body fluids, although in minute amounts (about 0.3–0.5 μg/g tissue).[32] They are present in adipose tissue, thymus, kidney, lung, spleen, iris, thyroid, adrenals, central nervous system, stomach, ovary, uterus, menstrual fluid, amniotic fluid, placenta, umbilical cord, etc. The presence of the biological activity, at least in low concentrations, in all tissues investigated suggest that these compounds have a biochemical role fundamental to many, perhaps all, cells. They have a highly diverse and potent biological activity depending on which type

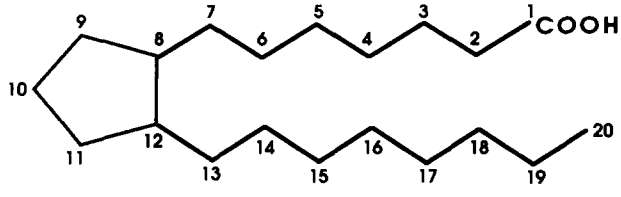

Figure 1 Prostanoic acid.

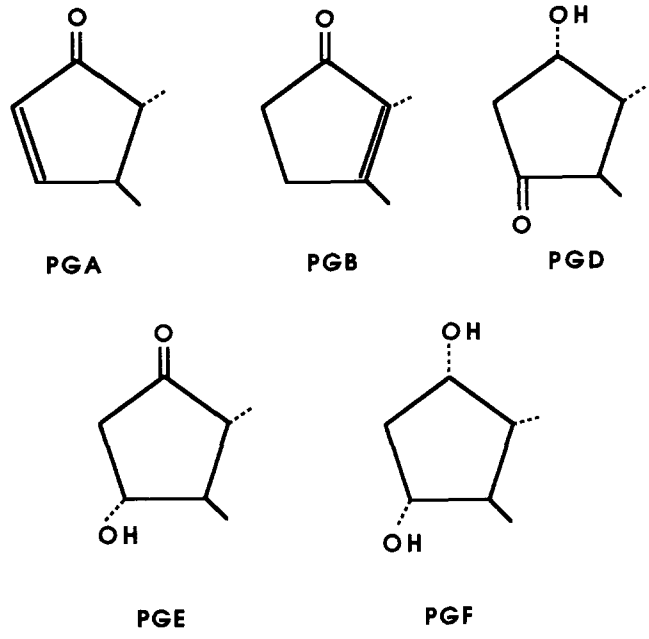

Figure 2 The ring structures of prostaglandins.

of PG is concerned with which tissue or organ. The type of PGs present in each tissue may vary, e.g., menstrual fluid has primarily PGE_2 and $PGF_{2\alpha}$, while amniotic fluid contains a mixture of PGE_1, $PGF_{1\alpha}$, PGE_2, and $PGF_{2\alpha}$ throughout pregnancy, and $PGF_{1\alpha}$ is present in the lung. Human seminal fluid contains the greatest number of different PGs.[33,34]

Biosynthesis

The three 20-carbon polyunsaturated fatty acids (PUFA) derived from essential fatty acids are the immediate precursors of PGs. These are eicosatrienoic (dihomo gamma linolenic) acid for the 1 series, e.g., PGE_1, $PGF_{1\alpha}$, etc., eicosatetraenoic (arachidonic) acid for the 2 series, and eicosapentaenoic acid (EPA) for the 3 series of PGs. These precursors are normally not found in the free state to an appreciable extent in the cell, but occur as components of phospholipids, neutral lipids, and cholesterol esters. Membrane phospholipids are rich in these PUFA, which are preferentially located in the carbon 2 position of the phosphoglyceride and serve as storage depot for the precursor fatty acids used for PG synthesis. The most common forms of PGs in mammalian tissues are of the 2 series, which probably reflect the greater abundance of arachidonic acid (AA) over the other two fatty acids in tissue lipids.

PG biosynthesis can be considered in three stages: (1) the release of 20-carbon fatty acid from cell membrane bound phospholipids in response to cellular stimuli; phospholipase A_2 has been shown to be important in the release of free fatty acids from phospholipid[35]; (2) the oxidation of the fatty acid to yield the intermediate endoperoxides; and (3) the cell-specific conversion of endoperoxides to the biologically active PGs.

Perturbance of the cell membrane, including very

slight chemical or mechanical stimulation is sufficient to activate the enzyme phospholipase A_2,[35,36] and possibly other specific lipases.[37] This appears to be the rate-limiting step in the biosynthesis of PGs because the free fatty acid is readily converted to PGs and related compounds depending on the nature of the tissue involved.[16] Phospholipase A_2 is a membrane-bound enzyme found in virtually every cell type and organ in the body. The synthesis is carried out by a membrane-bound prostaglandin synthase complex *(Figure 3)*, which has two subunits. The cyclooxygenase component[38] catalyzes the cyclization of carbon atoms 8 and 2 of the fatty acid and the enzyme requires two molecules of oxygen to form the cyclic endoperoxide. The two atoms of the first oxygen molecule attach to carbon 9 and 11, and a single atom of the second oxygen attaches to carbon 15 to form 15-hydroperoxide, PGG.[39,40] The subscripts on PGG, e.g., PGG_1, PGG_2, PGG_3, and their further products of metabolism (PGHs and PGs, etc.) depend, respectively, on their immediate precursor PUFA, dihomo-gamma linolenic acid (DHGL), AA, and EPA. The hydroperoxidase (second component of the enzyme complex) quickly converts PGG to PGH by the reduction of the hydroperoxide group to form an alcohol group at C_{15}. Both the subunits of the enzyme complex show an indistinguishable pH profile, heat stability, isoelectric point, and heme requirement. It has not been possible to separate the two proteins and it is assumed that the same enzyme protein catalyzes the two reactions. One thing that distinguishes the two enzyme activities is that the non-steroidal anti-inflammatory agents such as aspirin and indomethacin selectively inhibit cyclooxygenase activity[41,42] but not hydroperoxidase.

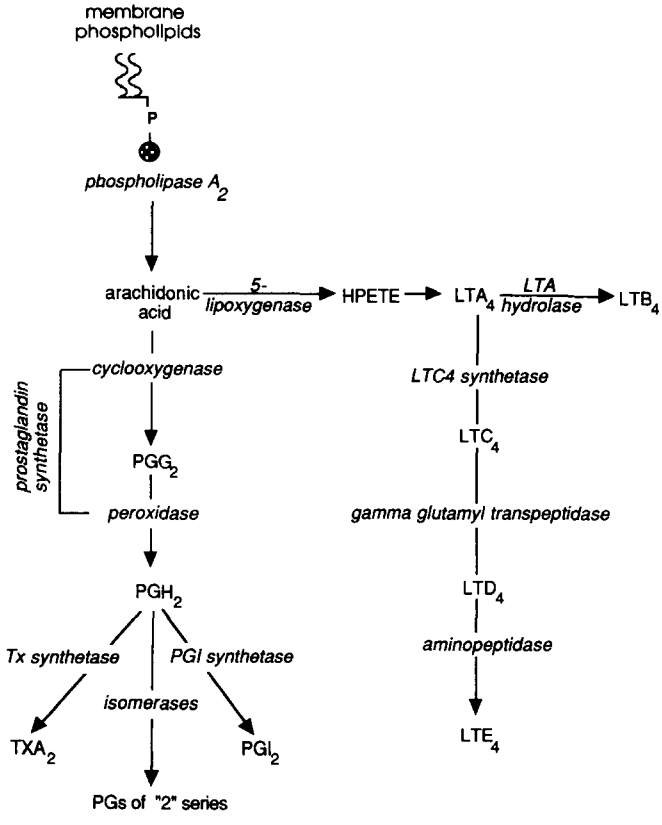

Figure 3 Formations of eicosanoids. In the case of DHGL (dihomogamma linolenic acid) in place of arachidonic acid, the products formed via cyclooxygenase pathway are PGG_1, PGH_1, TXA_1, and PGs of "1" series. When EPA (eicosapentaenoic acid) is the substrate, the products are PGG_3, PGH_3, TXA_3, PGs of "3" series, and PGI_3. In the lipoxygenase pathway EPA produces LTB_5, LTC_5, LTD_5, and LTE_5, and the products of Mead acid are LTA_3, LTC_3, LTD_3, and LTE_3. HPETE (5-hydroperoxyeicosatetraenoic acid); LT (leukotriene); PG (prostaglandin); PGI (prostacyclin).

PGH is the direct precursor for the synthesis of various types of PGs, thromboxanes, and prostacyclins. In contrast to prostaglandin synthase complex, including cyclooxygenase, which is distributed in various tissues, a specific PG endoperoxide metabolizing enzyme (or enzymes) is located in each tissue and produces a particular type of PG or a related component that regulates the function of the tissue with its specific biologic activity. In other words, most cells become highly selective in their metabolism of PGH to the biologically active product. This selectivity is usually linked to the function of the cell and its communication with cells that carry receptors for that specific PG, thromboxane or prostacyclin. All the active metabolites of the PGH, as a group, have been termed prostanoids. Prostanoids, as well as other biologically active metabolites of 20-carbon fatty acids, are also known as eicosanoids.[43] The enzyme PGH-PGE isomerase, which converts PGH to PGE,[44] has a wide distribution among organs and the seminal vesicles, the kidney medulla and cortex are particularly rich sources. The enzyme that catalyzes the isomerization of PGH to PGD is known as PGH-PGD isomerase,[45] and the one that converts PGH to PGF is known as PGH-PGF isomerase.[46] The conversion of PGE to PGF is catalyzed by prostaglandin 9-keto reductase that is found ubiquitously in the tissues of humans[47,48] and several other species.

Catabolism of prostaglandins

PGs are rapidly metabolized by a variety of tissues to compounds possessing reduced or no biological activity.[49] Lung, liver, and kidney appear to be the major sites of this degradation. In addition, during pregnancy placenta also has the ability to catabolize the PGs. Infused PGE_1, PGE_2, and $PGF_{2\alpha}$ disappear from blood after one passage through the lungs.[50,51] The first step in the metabolism of PG is the dehydrogenation of the C_{15} hydroxyl group by the NAD-dependent 15-hydroxy prostaglandin dehydrogenase,[52–54] a cytoplasmic enzyme, which catalyzes the conversion of PGs to their oxo derivatives. This is followed by reduction of the C_{13} double bond by prostaglandin reductase.[50,51] The resulting compounds are biologically inactive. Beta oxidation of the carboxyl side chain, omega hydroxylation at C_{20} followed by omega oxidation of the alkyl side chain, results in a compound that contains big and short chains terminating in a carboxyl group and is the

main urinary metabolite of PGE_1 and PGE_2.[55] A similar sequence operates for $PGF_{1\alpha}$ and $PGF_{2\alpha}$.[56] Because PGs act close to or at their site of synthesis and are rapidly metabolized, they are not considered to be circulating hormones.

Biological effects

PGs are highly active compounds that play important roles in several aspects of human physiology. Some of the relevant actions to the normal physiologic and pathologic conditions follow.

Vascular. PGs of the E series are potent vasodilators. When administered intravenously to a number of different species, including humans, PGEs lower the arterial pressure by causing general venous vasodilation, and this is accompanied by an increased cardiac output and heart rate. However, the vasodilatory effect depends on the route of administration. Given intravenously PGEs dilate the cerebral basilar artery, but when applied topically to the same blood vessel they produce vasospasm. But, the mechanism for the opposite effects of these PGs on the vascular system is not known.[57,58] $PGF_{2\alpha}$ is a potent vasoconstrictor of both pulmonary arteries and veins in humans.[59] PGD_2 is the major PG produced by mast cells and is released in the process of mastocycte activation by allergic and other stimuli. It is a potent systemic vasodilator and pulmonary artery vasoconstrictor.[60] Although endoperoxide intermediates PGGs and PGHs are unstable in aqueous solution (with a half-life of about 5 minutes at 37° C) and can be readily converted to other products, these intermediates have intrinsic biologic activity. Both PGG_2 and PGH_2 contract vascular tissue and ocular, gastrointestinal, and bronchial smooth muscle.[61]

PGs may maintain the patency of the ductus arteriosus, which serves to bypass the nonfunctioning lung in the fetus. In newborn infants the elevation in the partial pressure of oxygen causes the ductus arteriosus to close and allows normal circulation to occur. In some premature infants, the ductus arteriosus may not respond to oxygen, and this lack of response may be corrected by administration of the inhibitor of PG production. In infants with pulmonary atresia and other disorders where ductal flow is necessary while these patients are being prepared for corrective surgery, PGE_1 infusion provides a means to keep the ductus arteriosus open.[62,63]

Reproduction. PGs may have important functions in the reproductive system of both sexes. These biologically active compounds are synthesized in the seminal vesicle, which is a rich source of the enzyme cyclooxygenase. The mean total concentration of PGs in human semen may be as high as 400 μg/mL. PGE_1 and PGE_2 may have a role in fertility. The PG content of human semen is sufficiently high to cause dilatation of the cervix and may facilitate sperm transport to the ovum.[64] Decreased concentrations of PGE_2 have been found in semen of men who are infertile despite having normal sperm count and motility.[65] PGs also may have a role in ovulation and menstruation. In the rat, injection of PGE_1 or PGE_2, either systemically or into the third ventricle or directly into the median eminence region of the hypothalamus, elicits a surge in plasma of luteinizing hormone (LH) concentration.[66] Because ovulation is brought about by the action of LH released from the pituitary, PGs may be involved in menstruation and may be responsible for some of the unpleasant symptoms of menstrual disorders such as dysmenorrhea. $PGF_{2\alpha}$ and PGE_2 occur in the menstrual blood.[67] The amniotic fluid contains only traces of PGE_1 and PGE_2 during early pregnancy, but at the end of pregnancy and during labor $PGF_{1\alpha}$ and $PGF_{2\alpha}$ predominate.[68] As the labor proceeds, amniotic fluid concentrations of PGE_2 and $PGF_{2\alpha}$ increase steadily.[69] $PGF_{2\alpha}$ has oxytocic properties and promotes labor. The administration of $PGF_{2\alpha}$ to women at any stage of their pregnancy causes powerful contraction of the uterus and expulsion of the fetus. Because of this property, $PGF_{2\alpha}$ has been used to cause abortion[70] or induce labor.[71]

Gastrointestinal tract. PGs are released in the gastrointestinal tract by stimulation of the vagus nerve. All the PGs cause contraction in vitro of the longitudinal smooth muscle of the stomach and intestine, but the PGs of E type relax the circular muscles of the stomach and intestine and $PGF_{2\alpha}$ contracts these muscles. When injected, PGs greatly increase gastrointestinal motility and cause diarrhea. Relatively large amounts of PGs are present in gastrointestinal mucosa together with an enzyme responsible for their synthesis and degradation. PGs of the E series inhibit gastric acid secretion in humans and in experimental animals and prevent the formation of gastric and intestinal ulcers, caused by a number of surgical and chemical stimuli.[72] PGs are very potent cytoprotective agents.[73] The naturally occurring PGs are inactive when administered by mouth because of their very rapid catabolism in the gastrointestinal tract. This has encouraged the development of synthetic metabolically stable analogues, which are better suited to chronic administration in humans.[74–76]

Renal. PGE_2 and PGD_2 dilate renal blood vessels and increase blood flow through the kidney of most species.[77] They regulate sodium secretion and glomerular filtration rate. It is postulated that renal angiotensin and kinin system may activate phospholipase A_2 and thus release precursors of PG synthesis. The PGs are assumed to interact with the justaglomerular cells that regulate renin release.[78,79]

Inflammation. PGs occur in and around inflamed tissue. Pain, edema, and erythema are cardinal clinical signs of inflammation and evidence that these phenomena may be induced by PGs is compatible with their implication in the inflammatory processes. The involvement of PGs of the E type in inflammation is demonstrated by their proinflammatory effects and their generation in a variety of inflammatory situations, which

are curtailed by anti-inflammatory drugs. AA mobilization and endoperoxide and PG production during inflammation is well documented.[80-83]

Central nervous system. PGs are released in the central nervous system in response to electrical and chemical stimulation. Recently PGD_2 has been identified as the most prominent product in rat brain homogenates. It has been suggested that these compounds may have neurotransmitter function in the central nervous system.[60,84] PGE_2 is considered to play a role as central thermoregulator.[85]

Thromboxanes

Thromboxanes are classified into 1, 2, or 3 series depending on the number of double bonds and the A and B suffix describes the ring structure. Thromboxanes of the A type, which are formed from PGHs by the action of the enzyme thromboxane (TX) synthetase,[86,87] are highly unstable[87] in aqueous solution and are converted primarily to stable TXBs, which are biologically inactive. The product derived from PGH_1 by the action of TX synthetase is called TXA_1, but it is not of much significance because PGH_1 is a poor substrate for the enzyme.[88] TXA_2 *(Figure 3)*, which has a very short half life (30 seconds), is formed from PGH_2. TX synthetase has recently been purified from human platelets and found to be a cytochrome P-450 protein.[89] It is present in high concentration in platelets, and TXA_2 is the main metabolite of PGH_2 produced by these cells.[16] The enzyme is also found in leukocytes, human lung fibroblasts, spleen, lung, kidney, brain, and stomach. The platelets in blood have a tendency to stick to foreign surfaces (a process known as adhesion), and these cells also can stick to each other and form clumps (aggregation). TXA_2 is the most potent proaggregatory agent known and causes platelet aggregation.[87] It also strongly constricts blood vessels.[90] TXA_1, if formed, seems to have no such biological effects.[91] TXA_3 is formed from PGH_3, but is probably produced only in small amounts because EPA availability is normally limited. It differs somewhat from TXA_2 in its biological properties in that it is a vasoconstrictor like TXA_2 but has little platelet aggregating ability.[87]

Prostacyclins

Prostacyclin (PGI) is another addition to the family of compounds derived from PGH by the action of a membrane-bound PGI synthetase.[18] The enzyme is present mainly in the intima of arteries, but the lung[92,93] and stomach[94] are capable of synthesizing PGI. The enzyme seems to be located at two different sites within the same cell. In smooth muscle cells it is present at the inner surface of the plasma membrane and at the nuclear membrane.[95] The nomenclature for the PGIs is adapted from that of classic prostaglandins.[96] The compound PGI_1 cannot be produced biosynthetically from PGH_1 because the latter has no Δ^5 double bond. Therefore, it must lack a physiological role. It is chemically synthesized and used to produce antibodies to study PGI binding to cells.[97] PGI_2 *(Figure 3)* is derived from PGH_2 and is the main product of the cyclooxygenase cascade in the walls of the arteries and veins in several species, including humans. It is the most potent inhibitor of platelet aggregation and is also a powerful vasodilator of the coronary and other vascular beds. Thus, TXA_2 produced by platelets and PGI_2 formed by endothelial cells have diametrically opposite effects, yet both share the same biochemical precursor, PGH_2. Both compounds have been shown to exert their influence by regulating production of cyclic adenosine monophosphate (c-AMP). TXA_2 is an inhibitor and PGI_2 is a stimulus of c-AMP production.[98] PGI_2 is also unstable, and at pH of 7.5 and at 37° C it has a half-life of 2–3 minutes. It breaks down into a stable compound, 6, oxo-$PGF_{1\alpha}$.[99] PGI_3 that is formed from PGH_3 has vasodilatory and antiaggregatory properties similar to that of PGI_2.[100]

Leukotrienes

Leukotrienes (LTs) are a family of compounds formed from the 20-carbon PUFA by the action of 5-lipoxygenase. Several different LTs are found in the tissues, and they are identified by lettered suffixes A,B,C,D, and E, which refer to the order in which they are formed and also to the character of the substituents. The subscripts denote the number of double bonds present.[101] The most abundant naturally occuring LTs contain four double bonds and are synthesized from AA. The 5-lipoxygenase catalyzes the conversion of AA to 5-hydroperoxy eicosatetraenoic acid (HPETE), which is rapidly converted to an unstable epoxide called LTA_4.[102] Two metabolic routes are available to LTA_4 *(Figure 3)*: one is enzymatic conversion by LTA hydrolase to LTB_4; alternately it can be converted by the action of LTC_4 synthetase, a unique member of the family of glutathione-S-transferases, to LTC_4, which is the product of conjugation of LTA_4 with glutathione.[103] This enzyme is distinguished from other glutathione-S-transferases by its inability to use xenobiotic substances. LTC_4 can further be metabolized to LTD_4 by gamma-glutamyl transpeptidase[104] with loss of glutamic acid residue. The subsequent removal of glycine by aminopeptidase produces LTE_4.[105-107]

The 5-lipoxygenase and LTA hydrolase are cytosolic,[108] while the enzymes involved in the formation of LTC_4, LTD_4, and LTE_4 from LTA_4 are particulate.[109] It is now generally accepted that a mixture of LTC_4, LTD_4, and LTE_4 makes up the material originally known as SRS-A first described in 1938.[19,20] LTs of the "3" and "5" series can also be formed from eicosatrienoic (Mead) acid derived from oleic acid and EPA, respectively. DHGL lacks Δ^5 double bond and thus cannot react with 5-lipoxygenase. In the case of Mead acid that accumulates in essential fatty acid deficiency, the LTA_3 formed is a poor substrate for LTA hydrolase and is also a potent inhibitor of the en-

zyme.[110] Therefore no LTB_3 can be produced enzymatically. However, LTA_3 can be converted to LTC_3, LTD_3, and LTE_3.[111,112] LTB_5 as well as LTC_5, LTD_5, and LTE_5[113] can be formed from EPA.

The metabolism and inactivation of LTB_4 involves W-oxidation to give 20-OH and 20-COOH LTB_4 that can undergo extensive β-oxidation to give the final products, carbon dioxide and water.[27,114] The degradation of LTC_4 involves the conversion to LTE_4, resulting in some loss of biological activity.[115] The LTC_4, LTD_4, and LTE_4 can also be oxidatively metabolized with complete loss of activity.

The two groups of LTs, LTB_4 on the one hand and the cysteinyl LTs on the other, differ in biological activity.[116] LTB_4 has the leukocyte as its prime target whereas the cysteinyl LTs primarily affect smooth muscle and other cells with contractile capacity. LTB_4 is a potent chemotactic agent attracting neutrophils and macrophages to and causing aggregation at sites of infection or injury. It also causes lysosomal enzyme release and generation of superoxide in neutrophils,[117,118] and has an important role in inflammatory conditions and tissue damage. Synthetic LTB_3 has actions similar to LTB_4 and is equally potent in its biological actions,[119] while LTB_5 is 10- to 100-fold less active as LTB_4.[120,121] The cysteinyl LTs are potent vasoconstrictors and bronchoconstrictors. They increase permeability in postcapillary venules and stimulate mucus secretion. In terms of their effects on guinea pig ileum as SRS-A, LTD_4 is more potent and LTE_4 less potent than LTC_4.[27,118]

Lipoxins and metabolites of cytochrome P-450 action on AA

Lipoxins

In addition to the 5-lipoxygenase that is involved in leukotriene formation, there are two other lipoxygenases described in mammalian tissues: the 12- and 15-lipoxygenases.[122] The 15-lipoxygenase converts AA to 15-HPETE. Oxygenation (from the same or neighboring cells) and reduction yields two novel trihydroxy (5-, 6-, 15-, and 5-, 14- and 15-) compounds *(Figure 4)* with four conjugated double bonds, in contrast to leukotrienes, which have three conjugated double bonds. These compounds are positional isomers and designated respectively lipoxin A and B[123] (lipoxins-lipoxygenation interaction products). These metabolites express characteristic biologic properties in various experimental systems. They include contraction of lung parenchymal strips,[124] alteration of microvasculature,[124] modulation of natural killer cell activity,[125] generation of superoxide anion in human polymorphonuclear leukocytes,[123] and activation of protein kinase C.[126] Levels of lipoxin A are elevated in bronchoalveolar lavage fluid from certain patients with lung disease but not in healthy volunteers,[127] suggesting that this compound may play a role in the modulation of the inflammatory process. Lipoxins are also released in higher amounts from alveolar macrophages of virus-exposed rats,[128] and thus these eicosanoids may be involved in both pathophysiology and immunoregulatory network in virus-induced pulmonary disorder.

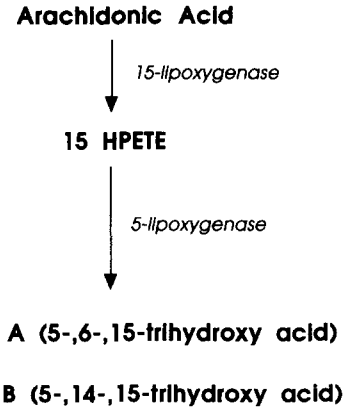

Figure 4 Formation of lipoxins.

Cytochrome P-450 metabolites

AA can also be metabolized by the cytochrome P-450 system, giving rise to several biologically active metabolites. The microsomal cytochrome P-450 represents a unique family of hemoproteins that serves as the terminal acceptor in the NADPH-dependent mixed-function oxidase system.[129] This system is comprised of cytochrome P-450, flavoprotein identified as cytochrome P-450 reductase, phosphatidyl choline, NADPH, and molecular oxygen. It catalyzes the oxidative transformation of a large number of lipophylic endogenous and xenobiotic substrates. The highest concentration of cytochrome P-450 is found in the liver, but several extrahepatic tissues contain this hemoprotein. Among them, kidney displays the highest concentration.[130] Cytochrome P-450 exists in multiple forms that differ in substrate specificity. This system catalyzes three types of reactions involving AA[30,131,132] *(Figure 5):* (a) olefin expoxidation leads to the formation of four (5,6-,8,9-,11,12-, and 14,15) epoxyeicosatrienoic acids (EETs). The EETs can undergo hydrolysis by epoxide hydrolase to form the corresponding dihydroxyeicosatrienoic acids (DHTs); (b) allylic oxidation leads to the formation of six cis-trans conjugated monohydroxy eicosatetraenoic acids (HETEs); and (c) W and W-1 hydroxylation gives rise to 20- and 19-HETEs, respectively; and 20-COOH-AA may arise from metabolism of 20 HETE.

The EETs and their hydrolytic metabolites, DHTs, possess a wide range of biological activities.[29,133,134] These include stimulation of hormone release from endocrine cells, inhibition of renal and corneal Na^+/K^+-ATPase, mobilization of microsomal calcium from aortic smooth muscle and anterior pituitary cells, inhibition of cyclooxygenase activity, vasodilation, inhibition of TX induced platelet aggregation, and regulation of ion transport and water handling in renal tubules. Of the four EETs, 5, 6 EET appears to be the most potent vasodilator and is dependent on endothelial cycloox-

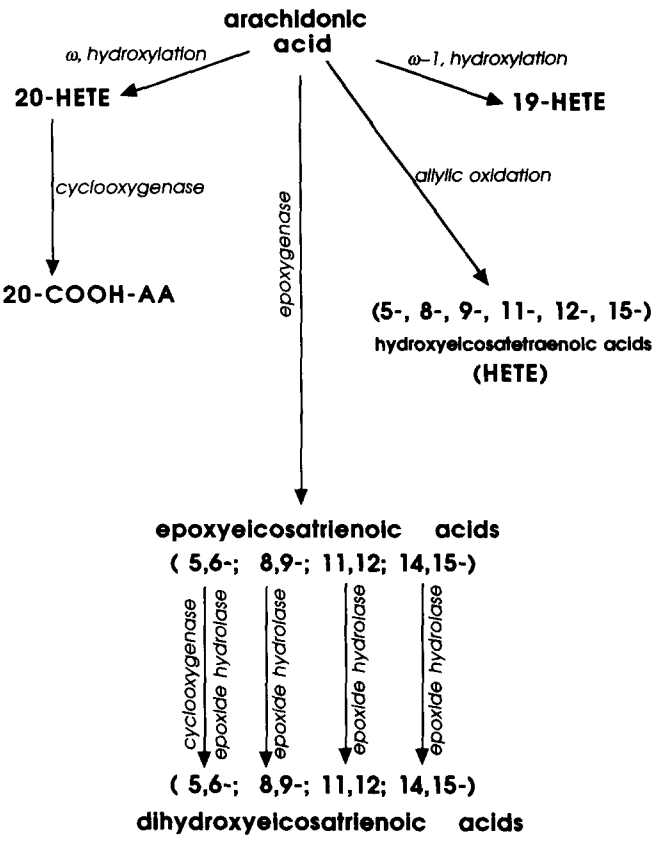

Figure 5 Arachidonic acid metabolism by cytochrome P-450–dependent reactions.

ygenase for expression of its vascular activity.[135] HETEs inhibit Na^+/K^+-ATPase and renin release.[136] The 20-HETE is a potent cyclooxygenase dependent vasoconstrictor.[137] 20- and 19-HETEs have prohypertensive properties and have been implicated in the development of hypertension in spontaneously hypertensive rats.[138]

Most of the biological effects observed were in the in vitro system, therefore, the in vivo significance of these metabolites was in question. However, recent work has identified these compounds as endogenous constituents of some animal tissues and also demonstrated their presence in human platelets, kidney cortex, and urine.[133,139,140] The urinary excretion of EETs was found to increase during pregnancy and a further increment was observed in pregnancy-induced hypertension.[141] Among the cytochrome P-450 metabolites of AA in the rat liver, EETs account for about two-thirds of the total. In the renal cortex, EETs represent 60%, whereas in the medulla, 19- and 20-HETEs make up about 90% of the total cytochrome P-450 metabolites. About 92% of the total rat liver EETs are found in cellular glycerolipids,[142] mostly in the phosphatidyl inositol, esterified to the carbon 2 position of the glycerol moiety. The cells can potentially release the preformed active metabolites, perhaps by the action of phospholipase A_2 and independent of the oxidative metabolism of AA. This is in contrast to the cyclooxygenase- and lipoxygenase-generated eicosanoids, which are quickly inactivated after formation and are not stored in any significant amount in tissues. Several glycerolipids serve as building blocks of cellular membranes and as mediators for the transduction of inter- and/or intracellular signals. Therefore, the presence of EETs in glycerolipids suggests that these AA metabolites may have a role in cell membrane functions. Indeed, exogenous addition of EETs to cultured rat glomerular mesangial cells does modify cell membrane permeability to peptide hormones and alter cellular concentration of H^+, Na^+, K^+, and Ca^{++}, perhaps by esterification of these metabolites to cellular glycerolipids.[29,30,143]

It is assumed that other PUFA may substitute for AA as substrates for cytochrome P-450–dependent reactions, but the substrate specificity requirements for metabolism by this system are not so narrowly defined as for cyclooxygenase and lipoxygenase pathways. However, it is becoming evident that the status of classic eicosanoids, e.g., PGs, TXs, PGIs, and LTs as modulators of cell function is to be shared with compounds formed in the newly discovered epoxygenase (cyt. P-450) pathway. The relative importance of this pathway within the family of eicosanoids and the differences in biological actions among metabolites derived from different PUFA are not known. This is an area of intense research that should contribute to our understanding of the role of cytochrome P-450 products of AA metabolism in human physiological and pathophysiological processes.

Inhibitors of eicosanoid biosynthesis

There are two types of drugs that affect the biosynthesis of eicosanoids: (a) the steroidal and (b) the nonsteroidal anti-inflammatory agents. The first step in the biosynthesis of prostanoids and leukotrienes is the release of AA (or other fatty acids) from membrane-bound phospholipid by phospholipase A_2. The steroidal anti-inflammatory agents, corticosteroids, inhibit phospholipase A_2 and consequently prevent the synthesis of PGs and other eicosanoids.[144–146] The main naturally occurring corticosteroids are cortisol (hydrocortisone) and corticosterone. Several synthetic corticosteroids have been developed, i.e., dexamethasone and prednisolone, and are used clinically.[147,148] The action of these steroidal agents is suggested to be by way of the synthesis of protein(s) called lipocortin(s), which inhibit(s) phospholipase activity.[149,150]

After the release from membrane phospholipid stores, 20 carbon fatty acid is enzymatically converted via the cyclooxygenase pathway to PG endoperoxides and then to PGs, thromboxanes and prostacyclins or via 5″-lipoxygenase to leukotrienes. The so called nonsteroidal anti-inflammatory (NSAI) agents inhibit cyclooxygenase enzyme activity.[151] The drugs in this group include aspirin (acetyl salicylic acid), indomethacin, fenoprofen, ibuprofen, and several others. Aspirin acts by acetylating a serine residue at the active site of cyclooxygenase and makes the inhibition of the enzyme

by this drug irreversible.[152–154] Therefore, PGs and other prostanoids can only be formed again after the new enzyme is synthesized. The other NSAI agents act reversibly on the cyclooxygenase.

Platelets do not normally adhere to healthy vascular endothelium. If the vessels are injured as a consequence of vascular turbulence, noxious chemicals, or physical trauma and cause the exposure of the subendothelial collagen fibers, platelets gather at the site of injury and initiate a process that promotes aggregation and the formation of thrombus or hemostatic plug. TXA_2 contributes to the intravascular aggregation of platelets. A controlling mechanism for platelet aggregation appears to be the balance between the formation of the proaggregatory TXA_2 by platelets and the antiaggregatory PGI_2 by endothelial cells in the cardiovascular system.[98] Too much TXA_2 generation or too little PGI_2 may cause thromboembolic disease.

One way to reduce the level of TXA_2 is to use substances that can specifically inhibit the formation of this prostanoid. Drugs such as imidazole[155] and its analogue dazoxiben[156,157] are known to inhibit TX synthetase, but so far these compounds have proved useful only as pharmacological tools for in vitro studies. Convincing in vivo data are not yet available, but dazoxiben is undergoing clinical trials and may have promising future as an antithrombotic agent.[158,159]

The most widely studied drug for its possible effect in reducing TXA_2 is aspirin, which irreversibly inhibits cyclooxygenase.[160] Theoretically, administration of this drug will inhibit the formation of not only TXA_2, but also of PGI_2 and other PGs in platelets, endothelial cells, and in all tissues. Therefore, it should not be of any benefit as far as the reduction in TXA_2 level is concerned because a simultaneous reduction of PGI_2 is also expected. But platelets are non-nucleated and have no ability to synthesize a new protein enzyme. The effect of aspirin to block cyclooxygenase, and hence of TXA_2 formation, will last for the life of the platelets in circulation, which is between 8–10 days in normal subjects. In contrast, endothelial cells that are nucleated can synthesize new cyclooxygenase, and the formation of PGI_2 can reverse relatively rapidly after aspirin administration, making the inhibitory effect of the drug short lived for endothelial cells. Aspirin also affects the cyclooxygenase activity in all other tissues involved in the formation of various PGs. Like endothelium, these tissues have the ability to synthesize a new protein enzyme and the drug's effect is assumed to be for only a limited time.

It has been suggested that intermittent administration of aspirin might optimize its antithrombotic potential. Because platelet cyclooxygenase may be particularly sensitive to inhibition by this NSAI agent, repeated administration of low doses of aspirin should show cumulative inhibition of TXA_2 formation without substantially affecting the production of PGI_2.[161,162]

Recent studies have shown that aspirin taken daily in doses of 325 mg, and even as low as 30 mg, is found to significantly reduce the risk of myocardial infarction.[163,164] Aspirin and other NSAI drugs prevent the formation of PGs, thromboxanes, and prostacyclins but they do not have an effect on lipoxygenase enzyme activity, except possibly to facilitate leukotriene formation by increasing the AA substrate. Some leukotrienes are vasoconstrictors. There are compounds such as benoxaprofen, isomaxazole, and others that are known to inhibit 5-lipoxygenase in vivo.[165,166]

PGI synthetase is inhibited by tranylcypromine, a clinically used antidepressant and brain monoamine oxidase inhibitor in vitro[167] and in cultured endothelial cells.[168] Nicotine is also a potent inhibitor of this enzyme in vascular tissues of rabbits and humans,[169,170] and it may be an important factor in association of smoking with the development of accelerated cardiovascular disease.

Dietary manipulation

The 20-carbon PUFA derived from dietary essential linoleic and linolenic acids–DHGL, AA, and EPA–are the natural substrates in tissues for the formation of eicosanoids. In most individuals subsisting on a Western diet there is an abundant dietary intake of preformed AA from meat products, and AA is the predominant constituent of most cell membrane phospholipids. Therefore, when tissues are stimulated or injured and phospholipases are activated there is release of AA that is converted to a number of eicosanoids, some of which, such as TXA_2 and LTs, have deleterious effects. Eicosanoids formed from DHGL and EPA in general have a favorable spectrum of biological activities. Dietary intake determines to a great extent the fatty acid composition of phospholipids in the plasma and cell membranes. There are several dietary constituents that can modulate the accumulation of PUFA in tissues and/or control the eicosanoid production.[171–173]

Dietary factors and formation of 20-carbon PUFA

Each type of dietary fatty acid influences the utilization of other fatty acids, and hence the composition of dietary fat is important in the metabolism of PUFA in tissues.[174,175] Linoleic, linolenic, and oleic (non-essential) acids are metabolized by the same sequence of enzymes with alternating desaturases and elongases.[176] The affinity of these fatty acids for the enzyme system is as follows: linolenic acid>linoleic acid>oleic acid.[177] As a result, the metabolites of oleic acid are normally found in minute amounts and the accumulation of C20:3,W9 (triene) is considered a marker of inadequate intake of essential fatty acids.[178] Oleic acid, when present in amounts 10 times greater than linoleic acid, suppresses the conversion of linoleate to AA and causes an increase in the triene:tetraene ratio in tissue lipids.[179] Supplementing the diet of healthy volunteers with oleic acid results in diminished AA content in platelet phospholipids, inhibition of platelet aggregation, and reduction in TXA_2 release.[180] Oleic acid is

the major fatty acid found in olive oil and this may in part explain why countries with high olive oil consumption have a low incidence of myocardial infarction. The conversion of linoleate to AA may be enhanced in certain tissues when the dietary intake of the former is reduced[181] and depressed by high levels of linoleate in the diet, as evidenced by the increased ratio of linoleic acid:AA in platelet lipids of animals fed high linoleic acid.[182] Seed oils such as corn oil, safflower oil, sunflower oil, etc. are rich in linoleic acid. Low concentrations of linolenic acid can suppress the metabolism of linoleic acid, while moderate levels of linoleic acid can inhibit the metabolism of linolenic acid.[183] A diet rich in saturated and monounsaturated fatty acids, at the expense of PUFA, induces the occurrence of eicosatrienoic acid in platelet phospholipids.[184] There is evidence that trans fatty acids present in hydrogenated fat can interfere with delta 6-desaturase (D-6-D),[185] the critical enzyme involved in the biosynthesis of long-chain PUFA.[176,186] In addition to the individual fatty acids, other factors may influence the formation of 20-carbon PUFA. For example, cholesterol affects the metabolism of PUFA and the production of eicosanoids by its inhibitory effect on delta 5- and delta 6-desaturases and stimulatory effect on delta 9-desaturase.[187–189] Alcohol inhibits D-6-D and causes increase in the ratio of linoleic acid:AA[190,191] in tissue lipids.

Naturally occurring fats and oils contain only minute amounts of DHGL, and this fatty acid is normally found at low concentrations in tissue lipids.[192] The tissue level of this fatty acid can be increased by taking gamma linolenic acid (GLA) or DHGL itself. A rich source of GLA is evening primrose oil, which contains about 9% of this acid.[193] It can further be metabolized in humans by chain elongation to DHGL and with further desaturation to AA. However, the conversion of DHGL to AA is very slow in humans. The advantage of taking GLA is that it bypasses the D-6-D enzyme. Dietary ingestion of 3 grams per day of evening primrose oil that contains about 220 mg of GLA has been shown to result in four- to nine-fold enrichment of platelets with DHGL and to favor synthesis of PGE_1 from stimulation of these cells.[194] Dietary supplementation with synthetic DHGL (usually as ethyl ester) is also found to increase the level of this fatty acid in platelet phospholipids and is correlated with modification of platelet aggregation observed in animals and humans.[195–197]

Linseed oil is a rich source of alpha linolenic acid (ALA), which makes about 59% of the total fatty acids. Rapeseed (including canola) and soybean oils and green leafy vegetables contain appreciable amounts of ALA. Feeding rats up to 4% of calories as purified methyl linolenate has been shown to decrease AA (23 to 11%) and to increase EPA from 0.1 to 3 to 4% in liver and serum lipids.[198] Ingestion of preformed EPA (3.6 g/day) for 4 weeks causes an increase of this fatty acid in platelet phospholipids[199] and reduces platelet aggregability and TXA_2 production. EPA and docosahexaenoic acid (DHA) are naturally abundant in the marine products and are thus present in significant quantities in fats and oils of edible fish.

Effects of 20-carbon PUFA fatty acids on eicosanoid formation

In contrast to AA, which is usually thought to be prothrombotic because of its ability to generate TXA_2, the prostanoids derived from DHGL are either neutral or very desirable in their biological actions. PGE_1 is an activator of cAMP formation, is a vasodilator, and inhibits platelet aggregation. Thus its actions are entirely antithrombotic in nature. Epidemiologic studies suggest a relationship between the risk of coronary artery disease and adipose tissue concentration of DHGL. In one study DHGL level was shown to be significantly lower in humans with newly diagnosed coronary artery disease when compared with those without disease.[200,201] However, no clinical studies have proved that dietary intake of GLA or evening primrose oil actually reduces the incidence of coronary artery disease. DHGL can reduce platelet TXA_2 production by competing with AA at the cyclooxygenase level so that PGH_2 is replaced by PGH_1, which is converted to prostanoids of "1" series and perhaps by inhibiting TX synthetase.[202] Another benefit of DHGL is that this fatty acid is only sparingly (less than 6%) converted through platelet TX synthetase to TXA_1, which has in any case very weak biological effects.[203] A major drawback of dietary DHGL, however, is its inability to form PGI_1 due to lack of required Δ_5 double bond. For the same reason, DHGL also is not a substrate for 5-lipoxygenase, the first enzyme that participates in the formation of LTs. Instead, this fatty acid is converted to a 15-hydroxy derivative that potentially blocks the formation of LTs from AA.[204,205] This suggests that a diet-derived DHGL is a potential endogenous modulator of LT synthesis and LT-associated diseases. Thus, high DHGL and low AA may be equally important as high EPA and low AA.

The most exciting development in the area of dietary fat in recent years is the potential benefit of ω-3 fatty acids in fish and fish oils. Epidemiologic studies have provided data associating seafood consumption with reduced risk of coronary heart disease and inflammatory disease.[206–208] Seafood is rich in the two ω-3 fatty acids EPA and DHA, and low in AA. Clinical studies have shown that the exchange of marine fish oil for vegetable oil in an otherwise typical Western diet leads to a more favorable pattern of serum lipids.[209] ω-3 dietary supplementation leads to a decrease in platelet TXA_2 formation[210–212] and an increase in those of TXA_3 and endothelial PGI_3.[213,214] The replacement of proaggregatory and vasoconstrictory TXA_2 with TXA_3, which is much less potent in both respects, leads to a shift in the TX/PGI balance, and this may produce the antithrombotic state. EPA is a poor substrate for cyclooxygenase and both EPA and DHA competitively inhibit the formation of prostanoids derived from AA. EPA is a good substrate for lipoxygenase and forms LTs. LTB_5 produced is far less

active than LTB_4 (from AA) in inducing neutrophil aggregation, chemotaxis, chemochinesis, and lysosomal enzyme release from neutrophils.[120,215] However, LTC_5, LTD_5, and LTE_5 are similar in potency to LTs derived from AA in inducing contraction of guinea pig ileum.[216]

Epidemiologic studies revealed that the incidence of chronic degenerative inflammatory disorders such as rheumatoid arthritis, psoriasis, and ulcerative colitis was lower in Greenland Eskimos than in Caucasians[217] and could be attributed to the high consumption of seafood by Eskimos. Clinical effectiveness of fish oils has been reported in rheumatoid arthritis,[218] psoriasis,[219] and ulcerative colitis. Fish oil ingestion reduced the formation of LTB_4 in stimulated neutrophils. Thus, supplementation of the diet with EPA or fish oil could, by reducing the proinflammatory eicosanoids, including PGE_2 and LTB_4, offer a non-toxic approach to the modulation of an anti-inflammatory response.

Effects of other dietary factors on eicosanoid formation

Various other dietary constituents may affect eicosanoid formation. Vitamin E and selenium (as part of glutathione peroxidase) act synergistically to protect the PUFA in membrane phospholipids from lipid peroxidation and thereby maintain the levels of precursors for the formation of eicosanoids. In vitamin E deficient rats, the release of PGI_2 in endothelial cells is reduced as a result of the accumulation of lipid peroxides that inhibit PGI synthetase.[220] In relatively high concentrations, vitamin E inhibits platelet aggregation[221] by preventing the accumulation of lipid peroxides and by inhibiting phospholipase activity.[222] Thus, administration of vitamin E could prevent and ameliorate vascular damage in some pathological states associated with accumulation of lipid peroxides in the vessels.[223] PGE_2 is known to suppress lymphocyte proliferation and interleukin-2 production. Vitamin E supplementation causes a decrease in PG production and a concomitant increase in interleukin-2 production and enhances cell-mediated immunity in animals[224] and humans.[225] This nutrient also can inhibit synthesis of lipoxygenase products, including LTB_4.[226] Vitamin C at concentrations of 3 mg/dL or greater is able to inhibit aggregation of platelets induced by AA, perhaps acting on TX synthetase.[227] In contrast, the deficiency of vitamin C shifts the formation of PGE_2 to the contractant $PGF_{2\alpha}$ in guinea pig tracheal muscle, suggesting that this nutrient may help modulate the contractility of the bronchial system.[228] Dietary deficiency of selenium also results in an increase in the synthesis of $PGF_{2\alpha}$.[229] Some compounds widely used as food antioxidants, such as butylated hydroxytoluene, butylated hydroxyanisole, α-naphthol, and propyl gallate,[221] have been shown to depress the formation of PGs from exogenous substrates even at low concentrations, while a variety of other antioxidants such as phenols and other aromatic and sulfhydryl compounds have a stimulating activity on PG production.[42] Certain essential macro- and microminerals may have a very important effect on key enzymes involved in eicosanoid formation.[230]

Recently there has been increasing interest in the beneficial effects of garlic, onion and ginger, the members of the *Allium* family.[231] In experimental and clinical studies extracts of these plants have been shown to inhibit platelet aggregation[232-234] and to lower blood pressure.[235] A compound with potential antithrombotic activity has been isolated and given the name "ajoune" after the Spanish word "ajo" for garlic.[231] This compound, as well as extracts of garlic, onion, and ginger, has been shown to inhibit platelet aggregation by blocking TX synthetase and thus reducing TXA_2 generation from AA.[232,236] Also, epidemiologic data in certain ethnic and geographic groups have shown that those who consume liberal quantities of garlic and onion have a lower incidence of cardiovascular disease.[237] The active component in garlic, onion, and ginger is reported to be a dual inhibitor. It affects cyclooxygenase[238] and lipoxygenase pathways[239] and provides relief in rheumatoid arthritis by reducing pain and improving the movement of joints in patients suffering from arthritis.[240]

Alcohol in concentrations as low as 10 mg% inhibits platelet TXA_2 synthesis and potentiates vascular PGI_2 synthesis.[241-243] These observations, together with the effect of alcohol on D-6-D,[190,191] are of interest because moderate alcohol ingestion is thought to offer some protection against cardiovascular disease.[244]

The cytochrome P-450 system is inducible by many chemicals and drugs, some of which are substrates for these enzymes. Well-known substrates in this category include barbiturates and the polycyclic aromatic hydrocarbons found in cigarette smoke. Some constituents in a normal diet such as the indoles present in cruciferous vegetables, e.g., cabbage, brussel sprouts, induce this enzyme system. Also, the way the food is cooked, such as charcoal broiling, can influence enzyme activity.[245] Because phosphatidyl choline is an essential component of the cytochrome P-450 system, dietary sources of PUFA, such as corn oil, have an effect on these enzymes.[246] But, different forms of cytochrome P-450 isoenzymes are induced by different inducers or induced under different physiologic conditions. For example, the production of 16-, 17-, and 18-HETEs by liver microsomes can be increased by treatment with B-naphthoflavone, which has the additional effect of reducing formation of EETs while enhancing that of 19-, and 20- HETEs.[247]

Dietary enrichment with fish oil is known to lower blood pressure in individuals with hypertension. Alteration in the production of prostanoid components by EPA is suggested to be the mechanism for a favorable effect of this PUFA on blood pressure. However, the observations of Knapp[248] suggest that the prostanoids may not be the primary mediators of blood pressure reduction by fish oil. Healthy male subjects ingesting fish oil supplements excrete in the urine increased diols of EPA, analogous to those formed from AA by cytochrome P-450, and decreased levels of AA

metabolites of the cytochrome P-450 pathway.[249] In view of the effect of some of the AA metabolites in this pathway on blood pressure, it appears that the corresponding metabolites derived from EPA may be responsible, at least in part, for the blood pressure-lowering action. EPA also may cause reduction in cytochrome P-450 metabolites of AA with deleterious effects on blood pressure. This study shows that EPA indeed can be metabolized in humans by the cytochrome P-450 pathway, and that it is possible to modulate the AA metabolism in this pathway by diet.

Conclusion

Eicosanoids are derived from 20-carbon PUFA, e.g., DHGL, AA, EPA, and Mead acid, which are components of membrane phospholipids. Because of the abundance of preformed AA in the Western diet, this fatty acid is most common in tissue phospholipids and the eicosanoids derived from it predominate in human tissues. Some of these eicosanoids, such as TXA_2 and LTs, have deleterious effects, but those formed from other PUFA are, in general, less potent. The production of these biologically active substances can be reduced by steroidal anti-inflammatory agents such as cortisone, which inhibit the release of precursor PUFA from phospholipids. Nonsteroidal anti-inflammatory agents such as aspirin inhibit cyclooxygenase and prevent the formation of all prostanoids. There are also specific compounds that act on individual enzymes in the cyclooxygenase and lipoxygenase pathways. These compounds are of interest as a therapeutic strategy in certain clinical conditions, such as cardiovascular and inflammatory diseases. It is possible to modulate the precursor fatty acid component in membrane phospholipids by dietary means, which in turn can alter the types of eicosanoids produced endogenously. Population and intervention studies suggest that ω-3 fatty acids present in marine lipids, fatty acids present in evening primrose oil, and oleic acid present in olive oil may have a number of potentially beneficial effects in the prevention and/or treatment of vascular and inflammatory diseases.

Vitamin E, vitamin C, and some other food antioxidants are known to depress the production of eicosanoids. Some essential minerals have important effects on enzymes involved in eicosanoid formation. In addition, substances present in garlic, onion, and ginger can modulate cyclooxygenase and lipoxygenase pathways, inhibit platelet aggregation, and provide relief in rheumatoid arthritis. Alcohol in moderate doses affects the formation of precursor 20-carbon PUFA and also inhibits TX synthetase. Several substances present in a normal diet, chronic alcohol consumption, and cigarette smoke can induce the cytochrome P-450 system and may in turn affect the formation of AA metabolites in this pathway.

Dietary manipulation can reduce the endogenous production of eicosanoids derived from AA and increase the generation of compounds with more favorable properties. The dietary approach may serve as a long-term preventive strategy and may lead to favorable modification of Western dietary habits.

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