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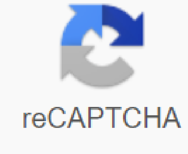

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Eicosanoids nutrition function

Skip Nav Destination Arachidonic Acid (AA) is an unsaturated fatty acid constituent in phospholipid domain cell membranes. It is subject to release via mobilization of phosflipases, especially a cytoplasmic phospholipase A2. Thereafter, it can be metabolized with at least two cyclooxygenase (COX) isoforms into prostaglandins and related compounds, via lipoxygenases to leukotrienes and via p450-catalyzed metabolism into epoxyeicosatrienoic acids. Collectively, these bioactive lipids are termed eicosanoids. All of these lipids express potent bioactivity in vitro. Clinical studies have already shown the importance of COX and lipoxygenase (LOX) products in human diseases. The generation of models of COX, LOX and prostaglandin receptor gene inactivation is likely to broaden our understanding of the importance of these compounds in vivo. Crystallisation of the biosynthetic enzymes is likely to facilitate the development of very specific inhibitors, as is the case already for COX-2. AA possesses inherent biological properties. It is also subject to free radical attack, generating isomeric eikosanoid species, the isoeicosanoids. These compounds can also express biological activity in vitro, although their importance in vivo is unclear. The development of specific analyses for these compounds in the urine suggests their benefit as a noninvasive index of oxidant stress in vivo. In 1934, von Euler identified a lipid-soluble substance from semen that would stimulate the smooth muscle contractions of the uterus and named it prostaglandin (von Euler 1934). Bergström and Sjovall (1960) isolated prostaglandin E from sheep prostate glands and showed that it was a 20-carbon acid with blood pressure-lowering activity. Bergström et al (1964) showed the enzymatic conversion of arachidonic acid to prostaglandin E2. Since arachidonic acid is synthesized from linoleic acid in humans, these discoveries established prostaglandins as a product of the metabolism of essential fatty acids. EICOSANOIDS: FORMATION AND BIOLOGICAL ACTIVITY It is now known that arachidonic acid (AA)4 is subject to metabolism by a wide range of bioactive lipid meditators. Two isoforms of prostaglandin (PG) G/H synthase, colloquially called cyclooxygenases (COX), catalyze the formation of PG and related compounds. Vane (1971) first showed that COX was the target of aspirin inhibition of PG formation. Inhibition of COX-1 in platelets, with consequent suppression of platelet formation (Tx) A2, is responsible for the effect of aspirin in the treatment of platelet-dependent callonhylene (Patrono 1994). Although the expression of COX-1 can be regulated, it is usually expressed in the form. Similarly, although COX-2 expression may be beneficial, especially in the cells of the reproductive tract and in the nervous system (Yamagata et al. 1993), its expression is usually regulated, in particular by cytokines, growth factors and tumour promoters (Fu et al. 1990). These observations have implicated COX-2 in the PG generation in inflammation and, perhaps, cancer (Tsuji et al. 1997). COX-1, on the other hand, is expressed consistently in the normal epithelium. Inhibition of COX-1 is thought to underlie the gastrointestinal side effects of widely available nonsteroidal anti-inflammatory drugs (NSAIDs), all of which are quite nonselective between the two COX isoforms (Smith et al. 1996). The development of highly selective COX-2 inhibitors (Seibert et al. 1994) can thus promise compounds that are better and more effective than conventional NSAIDs. One potential warning is that an induced inflammatory response is impaired in mice deficient in COX-1, but not COX-2. The latter mice were also able to mount an inflammatory response to temporary infection (Langenbach 1995; Morham in 1995). Both COX isoforms have now been crystallised (Browner 1996, Loll et al. 1995). Although G protein-coupled receptors for all PG have been cloned (Narumiya 1994), only the human pharmacology of specific antagonists of the TxA2 receptor (TP) has been characterized to date. It is likely that the latest generation of mice that are deficient in each of these receptors will further shed light on their in vivo biology. Similarly, there have been suggestions that eicosanoids can activate nuclear receptors (Forman et al. 1997). However, questions of specificity and concentration-response relationships with compounds actually formed in vivo need to be resolved. Lipoxygenases generate leukotrienes and related compounds. These lipids express biological properties of likely relevance to inflammatory reactions in vivo. This is consistent with the phenotype expressed by mice deficient in the 5-lipoxygenase enzyme (Chen et al. 1994). Specific antagonists of sulfidopeptide leukotrienes have found efficacy in human asthma, which has specific inhibitors of 5-lipoxygenase (O'Byrne 1994). Leukotrienes and related compounds have also been involved in neuronal function, atherogenesis, cellular proliferation and the regulation of vascular tone in vitro. Again, the recent availability of mice deficient in specific lipoxygenases can clarify the in vivo relevance of these observations. Much less is known about the biological significance of the catalysed epoxyogenase's catalysed formation of epoxycosatrienoic acids (EET) and related products, probably through p450 isozymemes with high affinity for arachidonic acid as a substrate (McGiff 1991). These compounds are potent regulators of epithelial ion transport and vascular tone in vitro (Oyekan et al. 1994). However, specific receptors for EET have not yet been cloned, and animals deficient in the AA-specific p450 isoforms (Wu et al. 1996) have not yet been generated. Data suggesting their importance in hypertension have been inhibitors (Makita et al. 1994). However, given the absence of a specific agent for pharmacological inhibition of their synthesis or effect, their role in pathophysiology is currently speculative. In addition to these observations, cells can interact to generate new transcellular products of AA (Marcus 1990). Similarly, AA itself can directly modify cellular function. Arachidonoylation of cellular proteins such as G proteins (Hallak et al. 1994) or miniglucagon (Sauvadet et al. 1997) can thus modify their effects. It can directly regulate ion channels (Damron et al. 1993) or influence gene expression (Barry et al. 1997). Differential allosteric regulation of the two COX isoforms by AA can cause dramatic differences in isoform selectivity for inhibitors, as a function of AA concentration (Swinney et al. 1997). A current area of interest has been the potential importance of oxidized lipids in the modification of cellular function (Lehr et al. 1997). The focus of this review will be on candidate members of this species, a family of free radicals–catalysed products of arachidonic acid, the isoeicosanoids. ISOEICOSANOIDS Isoeicosanoids, isomers of enzymatic derived eicosanoids, are free radical-catalysed products of arachidonic acid (Nugteren and Christ-Hazelhof 1980, O'Connor et al. 1984). The presence of The F2 isoprostans, isomerer of PGF2α, in human plasma and urine was first described by Morrow et al. (1990). More recently, the free radical-dependent formation of E2 and D2 isoprostanes, isothromboxanes and isoleuectrienes has been reported. Four classes of F2-isoprostanes (IPF) have been described (Fig. 1; Waugh and Murphy in 1996). The relative abundance of formation of specific isomer in vivo is unknown, but to date, the most closely studied is a member of the IPF-IV class, 8-epi PGF2α. This potent vasoconstrictor and mitogen are present in atherosclerotic plaques, but not in healthy vascular tissue (Pratico et al. 1997). These effects of 8-epi PGF2α are blocked by thromboxane receptor antagonists. Unlike thromboxane analogues, 8-epi PGF2α induces platelet form change without irreversible aggregation; it also operates with threshold concentrations of conventional agonists to induce an irrevocable aggregation (Pratico et al. 1996). However, high concentrations of 8-epi PGF2α are necessary to activate the cloned splice variants of the human thromboxane receptor; its importance as autaidat in vivo is unclear. Open in new tabDownload slideThe F2-isoprostane family of isomers can be divided into four classes; 8-epi PGF2α belongs to Class IV and IPF2α-I to Class I. Although 8-epi PGF2α is a minor by-product of cyclooxygenase (COX) pathways in vitro, there is no evidence that IPF2α-I can be generated in this way. DIFFERENTIAL ISOPROSTANE FORMATION Rather than estimating the formation of total F2 isoprostan by using internal standard, we have developed specific analyses for discrete members of the IPF classes (Pratico et al. 1995). Initially, we focused on the formation of 8-epi PGF2α of human platelets and monocytes in an attempt to characterize the mechanisms of the isoprostane generation. To our surprise, we found that the 8-epi PGF2α, but not other F2 isoprostanes, could be formed as a minor product of the COX-1 enzyme in platelets and cox-2 isoform monocytes (Pratico et al. 1995, Pratico and FitzGerald 1996). These were potentially important observations, because activation of platelets or monocytes may be a feature of many syndromes putatively associated with oxidant stress. However, administration of an aspirin regimen, aimed at inhibiting platelet COX-1, failed to suppress the elevated urinary 8-epi PGF2α levels that we observed in chronic smokers (Reilly et al. 1996a), a syndrome of COX-1 activation. The same regimen suppressed significant secretion of the 11-dehydro metabolite of thromboxane B2, which is largely derived from platelets. Thus, the capacity of platelets to form 8-epi PGF2α in a COX-1-dependent manner did not seem to contribute measurably to the urinal index for overall 8-epi PGF2α biosynthesis. It is unknown to what extent, if any, COX-2-dependent pathway may contribute to the formation of 8-epi PGF2α in settings of inflammation and cellular proliferation, where COX-2 induction can be expected. Despite the apparent lack of relevance of the enzymatic formation of 8-epi PGF2α to the use of its urinary excretion as an index of oxidant stress, it seemed wise to develop methods for measuring another F2 isoprostane that was not susceptible to enzymatic formation. IPF2α-I is a member of a distinct class of F2 isoprostanes (Waugh and Murphy 1996). It is not formed by COX and its excretion in volunteers is not suppressed by aspirin (Pratico et al 1998). Urinary levels of IPF2α-I and 8-epi PGF2α are closely correlated (r = 0.57, P < 0.0001) in patients with hypercholesterolemia (Fig. 2). This is a setting of moderate COX-1 activation. These observations are consistent with the hypothesis that excretion of both compounds in the urine reflects formation through a common mechanism—free radical-catalyzed generation of prostaglandin isomers. It thus appears that the enzymatic formation of 8-epi PGF2α of COX is a trivial contributor to overall 8-epi PGF2α biosynthesis in vivo and should not detract from its usefulness as an index of oxidant stress. Open in new tabDownload slideThe ratio of urine 8-epi PGF2α to IPF2α-I levels in normocholestrolemic controls and patients with homozygous familial hyper-cholesterolemia (HFH). Correlation (r = 0.57, P < 0.0001; n = 109). ISOPROSTANES AND OXIDANT STRESS Oxidative stress is thought to play an important patophysiologic role in a variety of diseases of cancer and neurodegenerative disorders. However, the difficulty of assessing radical generation in vivo has proved to be the major limitation of our understanding of this mechanism of human disease. Traditional in vitro analyses, directed against malondialdehyde or lipid hydrhydroxides, are believed to be irrefactoricable when applied to clinical examination, due to such factors as ex vivo generation of products and both instability and nonspecificity of the analytes involved. Furthermore, it is unclear how ex vivo estimates of free radical generation, such as lipoprotein oxidizability or the formation of adducts detected by spin capture, relate to oxidant stress in vivo. The measurement of F2 isoprostans may represent an important development in the assessment of free radical generation and oxidant stress in vivo. They are remarkably stable compounds. Coordinating the elevation of plasma and urinisoprostanes in syndromes of extrarenal oxidant stress (Morrow et al. 1995, Pratico and FitzGerald in 1996) means that little is likely to be gained by measuring metabolites, rather than the parent products, in urine. However, estimates of 8-epi PGF2α in plasma, where there is an abundance of lipid, can be confused by its autooxidation ex vivo. In addition, COX-1-dependent platelet formation activated ex vivo may also undermine plasma-based measurements such as the index of actual formation of 8-epi PGF2α in vivo. Thus, the measurement of a metabolite of 8-epi PGF2α (Roberts et al. 1996) power to circumvent this problem, unless it is formed in the cells of circulating blood. We have used gas chromatography/mass spectrometry to validate immunoassays of the parent compound. More recently, we have adopted an integrated approach that uses the coordinate measurement of urine 8-epi PGF2α and IPF2α-I in the evaluation of oxidant stress in specific clinical settings. F2 ISOPROSTANES IN SPECIFIC CLINICAL SYNDROMES There is a dose-dependent increase in urine 8-epi PGF2α secretion in apparently healthy chronic cigarette smokers, who were not suppressed by aspirin. Both cessation of smoking, with the addition of nicotine patches and short-term therapy with vitamin C (2000 mg/d), an endogenous antioxidant, weakened the height of urine 8-epi PGF2α secretion. Deficiency of vitamin C (Heitzer 1996) can make smokers particularly susceptible to the antioxidant effects of exogenous vitamin supplements. Oxidation of LDL is thought to play a crucial role in atherogenesis. This hypothesis is largely based on indirect evidence. We have recently immunolocalized 8-epi PGF2α to monocyte/macrophages and vascular smooth muscle cells in human atherosclerotic plaques and demonstrated increased levels of this compound in atherosclerotic vessels, compared to normal arterial segments (Pratico et al. 1997). Furthermore, together with others, we have shown that F2 ldl when oxidized in vitro. Therefore, we have designed specific studies to assess the biosynthesis of both 8-epi PGF2α and IPF2α-I in patients with homozygous familial hypercholesterolemia (HFH) and also in more moderate hypercholesterolemia. Urinary excretion of these isoprostanes was increased in both groups of hypercholesterol patients compared to their respective controls. The concentration of 8-epi PGF2α was further elevated in LDL and correlated with urinary excretion of this compound in a subset of these patients (Reilly et al. 1996b). Given the potentially distinct mechanisms that can result in free radical generation in smokers, an even greater increase in dyslipideic individuals who smoke can be predicted. Interestingly, the exact role of dietary lipids in isoprostane biosynthesis in normal individuals or in the setting of increased biosynthesis remains to be addressed definitively. Oxidant stress has been involved in vascular reperfusion after a period of ischemia. Examples include the regional myocardial anesthetic seen in animal models of coronary occlusion/reperfusion and in some patients following thrombolytic therapy, as well as in the global myocardial dysfunction seen after coronary artery bypass surgery. We have shown increased urinary 8-epi PGF2α in a number of syndromes of myocardial reperfusion (Delanty et al. 1997). Levels were significantly elevated, coinciding with doppler-documented reperfusion, in a dog model of coronary thrombolysis. Similarly, excretion was improved coincident with cross-clamp release compared to preoperative and postoperative values in subjects undergoing elective coronary artery bypass surgery. Recently, we have expanded these studies to include patients undergoing reperfusion for myocardial infarction. Urinary excretion of 8-epi PGF2α and IPF2α-I was markedly increased cosied with angiographically documented reperfusion in patients treated with thrombolytic agents and percutaneous transluminal coronary angioplasty (PTCA) for myocardial infarction. There was a minor increment in isoprostane excretion after diagnostic coronary arteriography and elective PTCA. The metabolic disposition of isoprostanes in vivo remains to be investigated. However, our experience with indexes of eicosanoid biosynthesis suggests that urinary excretion may reflect either renal and extrarenal sources (or both) of isoprostane formation, depending on the experimental setting or disease during study. CONCLUSIONS Both enzymatic and nonenzymatic products of AA, as well as the substrate itself, have been involved as mediators in human biology. Generally, the importance of these bioactive lipids is expressed under pathophysiologic circumstances, in which they tend to subserve a homeostatic function. Inhibition of their biosynthesis can have positive effects. An example this is the anti-inflammatory effect of NSAIDs. Alternatively, the same intervention may have harmful consequences. One example is the worsening of renal blood flow in patients with renal compromise administered NSAIDs. Urinary excretion of these bioactive lipids may also be utilized to reflect cellular activation in vivo. Given that the products of enzymatic metabolism of AA express relative cellular specificity, secretion of distinct compounds or their metabolites may reflect activation of specific repertoires of cells. Examples include the use of Tx metabolites to reflect platelet activation and prostaglandin D (PGD) metabolites to reflect mast cell activation. Again, the relative contribution to what is excreted in urine is a function of the exact clinical condition during the study. Finally, interest is developed in the use of isoprostane excretion as a strategy for studying lipid peroxidation in vivo. 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Pharmakol.4445 Expression of a mitogen inducible cyclooxygenase in brain neurons: regulation by synaptic activity and glucocorticoids. Abbreviations homozygous familial hypercholesterolemia nonsteroidal anti-inflammatory drugs percutaneous transluminal coronary angioplasty Supplement Supplement

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