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Eicosanoids: essential mediators in health and disease

Eicosanoide: bedeutende Faktoren in der Homöostase und ihre Bedeutung in der Pathogenese multipler Erkrankungen

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Abstract

Eicosanoids are lipid mediators that are primarily oxidized from arachidonic acid by enzymatic or non-enzymatic peroxidation. The diverse and potent biological actions of eicosanoids on almost every cell reflect the central role of these mediators in maintenance of physiological homeostasis, of cell adhesion, vasomotion and organ functions. Eicosanoids were historically considered as terminal mediators, causing symptoms such as fever, pain, edema, smooth muscle contraction and inflammation. However, recent studies using gene knockout mice models for both enzymes and receptors have revealed that they also play a fundamental role in pathological processes and disease. Imbalance of the major lipid signaling pathways contribute to disease progression and chronic inflammation, autoimmunity, allergy, cancer, atherosclerosis, metabolic and degenerative diseases. A systematic, multiparametric eicosanoid analysis in various diseases could unravel the underlying biology and disease pathology, possibly resulting in new diagnostic and therapeutic strategies. The aim of our review is to discuss the different eicosanoid pathways and the impact of these essential mediators in human health and disease.

Keywords: arachidonic acid; eicosanoids; eicosanoid metabolism; eicosanoid pathways.

Zusammenfassung

Eicosanoide sind Lipidmediatoren, die durch enzymatische und nicht-enzymatische Peroxidation aus Arachidonsäure entstehen. Die vielfältigen biologischen Effekte auf Zell- und Organebene unterstreichen die zentrale Bedeutung dieser Mediatoren in der Zell-Homöostase. Zunächst wurden Eicosanoide als Effektoren in Zusammenhang mit Fieber, Schmerz, Ödembildung, Kontraktion glatter Muskulatur und Entzündung betrachtet. Insbesondere experimentelle Ansätze mit murinen Knock-out-Modellen für die an der Eicosanoid-Metabolisierung und Regulation beteiligten Enzyme und Rezeptoren, konnten einen entscheidenden Beitrag zur Einordnung dieser zentralen Mediatoren in die Pathophysiologie einer Vielzahl von Erkrankungen leisten. So konnte eine pathogenetische Bedeutung der verschiedenen Signalwege für die Entwicklung und Progredienz von allergischen, autoimmunen und auch chronisch entzündlichen Erkrankungen wie der Atherosklerose gezeigt werden, des Weiteren bei Malignität, degenerativen und weiteren metabolischen Erkrankungen. Eine systematische multiparametrische Analyse der verschiedenen Signalwege auf Mediatorenebene mit Hilfe der Tandem-Massenspektrometrie könnte die Rolle dieser Metaboliten für die Krankheitsentstehung aufklären und neue diagnostische und therapeutische Strategien ermöglichen. Ziel der Übersicht ist es, die verschiedenen Signalwege des Eicosanoid-Stoffwechsels darzustellen und die potentielle Bedeutung von Eicosanoiden in der Zell-Homöostase und der Pathogenese verschiedener Erkrankungen zu diskutieren.

Schlüsselwörter: Arachidonsäure; Eicosanoide; Signalwege des Eicosanoidstoffwechsels.

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Introduction

Eicosanoids are lipid signaling molecules that are primarily oxidized from arachidonic acid (AA) by the action of phospholipase A_2 (PLA_2) enzymes. The following enzymatically metabolization via cyclooxygenase (COX), cytochrome P450 (CYP450) and lipoxygenase (LOX) pathways or via non-enzymatic peroxidation allows the generation of a broad spectrum of different eicosanoids and isoprostanes (Figure 1). Although originally recognized for their capacities regulating vascular dilatation,

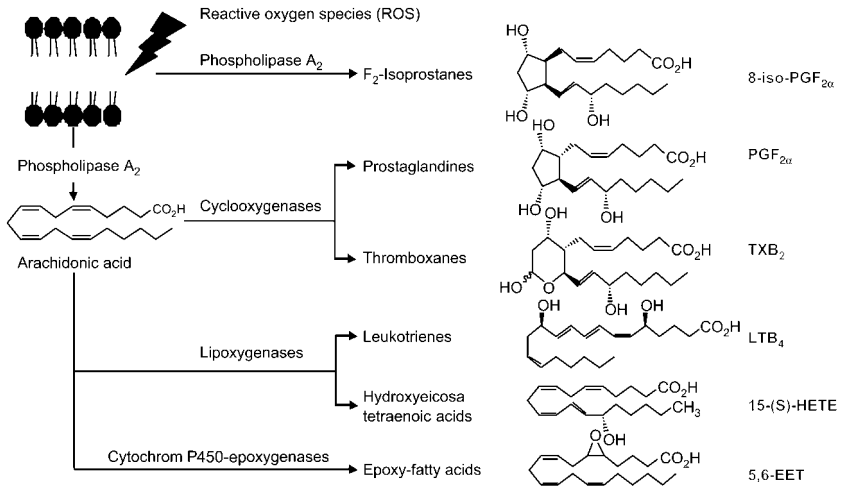

Figure 1 Eicosanoid biosynthesis from arachidonic acid.
Eicosanoids are lipid signaling molecules that are primarily oxidized from arachidonic acid (AA) by the action of phospholipase A_2 (PLA_2) enzymes. The following enzymatically metabolization via cyclooxygenase (COX), lipoxygenase (LOX) and cytochrome P450 (CYP450) pathways or via non-enzymatic peroxidation allows the generation of a broad spectrum of different eicosanoids and isoprostanes. Some representatives of each group are shown.

vascular permeability and platelet aggregation, eicosanoids are appreciated playing key roles in the immune response, in inflammatory, autoimmune and allergic diseases, in chronic tissue remodeling and in cancer. Furthermore, there is recent evidence that eicosanoids play an active role in controlling and programming resolution of inflammation by stimulating endogenous anti-inflammatory and proresolving pathways [1, 2]. Different eicosanoids show opposite biological effects, supporting the central role of these mediators in health and disease. Consistent with their biological importance, the synthesis of eicosanoids is strongly regulated, particularly via expression of specific cellular enzymes. The expression rate of various enzymes is affected by several exogenous factors, including cytokines, hormones, vitamins, microbial factors and gene variants in the promoter or coding elements of their corresponding genes [3]. Virtually all mammalian cells participate in eicosanoid synthesis, however, the expressed pathways and subsequently the eicosanoid response depend on the individual cell type. Cells of connective tissue or parenchymal cells such as epithelial cells, endothelial cells, fibroblasts and smooth muscle cells show the highest capacity for COX-associated eicosanoids. Bone marrow-derived cells tend to synthesize LOX-dependent metabolites. Eicosanoids are synthesized in a calcium-dependent manner from precursor membrane lipids. After secretion they exert their effects mainly locally through interaction with receptors on the cell surface or the nuclear membrane in an autocrine and paracrine manner. Predominantly, they are characterized by a short half-life from seconds to minutes and can be degraded both enzymatically and non-enzymatically [4]. The fundamental properties of eicosanoids are their stereo-chemical analogy, their mediator potency in the nanomolar range and their essential and multiple biological and antagonistic activities.

Prostanoid synthesis – the COX pathway

Prostanoids are formed by the action of COX, a highly conserved enzyme, existing in two isoforms, designated as COX-1 and COX-2. Both enzymes contribute to autoregulatory and homeostatic prostanoid generation. However, COX-1 appears to be the preferred source for basal prostanoid synthesis. COX-1 metabolites are involved in mediating homeostatic functions in health such as renal water and electrolyte balance, gastric cytoprotection and platelet aggregation. COX-2 is described to be the more important source of prostanoid formation in pathological conditions such as inflammation and cancer. Recently, experiments with transgenic mice revealed specific patterns of coupling between either COX-1 and COX-2, and even specific upstream PLA_2 and downstream prostaglandin (PG) synthases [5]. Via the COX pathway, AA is transformed to PGG_2 and PGH_2, which are subsequently converted into PGs and thromboxanes (TXs) by cell type specific PG synthases. In addition to monocytes and macrophages that synthesize a broad range of prostanoids, most other cell types are characterized by a single predominant COX product. Thus, platelets mainly secrete TXA_2, mast cells PGD_2, endothelial cells PGI_2 and epithelial cells; fibroblasts and smooth muscle cells primarily secrete PGE_2 [3]. Prostanoids might undergo facilitated transport from the cell through a prostanoid transporter or other carriers, mediating a variety of biological functions in almost all tissues through the activation of their cognate G-protein-coupled receptors [6]. PGE_2 and PGI_2 are predominant proinflammatory prostanoids, both

markedly enhance edema formation and leukocyte infiltration by promoting blood flow and vascular permeability. Activated platelets synthesize TXA_2, amplifying further platelet activation and recruitment and vasoconstriction. PGI_2 is the major platelet inhibitory prostanoid and one of the strongest vasodilatators [7]. Active prostanoids are rapidly metabolized to an inactive product. Prostanoids are not stored intracellularly but they are synthesized and released immediately. Thus, only small quantities of the active compounds are measurable in the systemic circulation during normal physiologic states.

Leukotriene synthesis – the LOX pathway

Leukotrienes (LTs) are predominantly synthesized by inflammatory cells such as polymorphonuclear leukocytes, macrophages, mast cells and dendritic cells [8]. Cellular activation by immune complexes, bacterial peptides and other stimuli elicit a cascade of cell activation events leading to biosynthesis of LTs. The synthesis of LTs from the substrate AA is initiated by 5-lipoxygenase (5-LO) in concert with 5-LO-activating protein (FLAP). The immediate product of 5-LO is LTA_4, which is enzymatically converted into either LTB_4 by LTA_4 hydrolase or LTC_4 by LTC_4 synthase. LTB_4 and LTC_4 are exported from the cell by specific transporter proteins, following subsequent conversion to further metabolites by amino acid hydrolysis [9]. An additional product for which synthesis is initiated by 5-LO activity is 5-oxo-HETE, which is found in leukocytes and platelets and represents a precursor for several additional eicosanoids [10]. Non-leukocyte cells generally do not have sufficient 5-LO and FLAP to synthesize relevant amounts of LTs directly from arachidonate. However, such cells expressing distal LTA_4-metabolizing enzymes can take up leukocyte-derived LTA_4 and metabolize it into bioactive LTs. These transcellular interactions can involve virtually any combination of bone marrow-derived and connective tissue associated cell types. An important example is the interaction between leukocytes and endothelial cells [11]. Unlike the COX enzymes, 5-LO as one of the main variables that influences LT synthesis, is typically inactive in resting cells. Upon cell activation, 5-LO associates with intracellular membranes, which presumably places it to FLAP and free AA. By ligating their specific cognate receptors (mainly G-protein-coupled receptors), LTs promote the accumulation and function of virtually all subgroups of leukocytes at sites of inflammation. LTB_4 as primary representative mediates the recruitment of mast cells, neutrophils, monocytes, macrophages and T-cells and induces the expression of adhesion molecules [11].

The cytochrome P450 pathway

Similar to LOXs, CYPs catalyze the hydroxylation and epoxygenation of AA, forming hydroxyeicosatetraenoic acids (HETEs) or epoxy-eicosatrienoic acids (EETs). One of the best characterized HETEs is 20-HETE, which has been shown to promote systemic vasoconstriction [12]. Other CYP-associated HETEs demonstrate considerable bioactivity that often act in opposition to 20-HETE, inducing vasodilatation [13]. More recently, 16-HETE has been demonstrated to inhibit neutrophil adhesion, suggesting an important anti-inflammatory role [14]. EETs have been implicated in several important biological processes, including vascular tone, renal function, leukocyte adhesion, neuronal signaling and angiogenesis [15].

Lipoxin synthesis

Multicellular host responses to infection, injury or inflammation stimuli lead to the formation of lipoxins (LXs), generated from AA via sequential actions of LOs during interaction of different cell types, in particular between neutrophils and platelets, or epithelial cells and leukocytes [16]. LXA_4 and LXB_4 are the main representatives, showing potent cellular and in vivo actions. Lipoxins are the first lipid mediators discovered that demonstrated anti-inflammatory activity as well as the capacity to promote the resolution of inflammation and return to tissue hemostasis via G-protein-coupled receptors [15]. The main actions of LXs are inhibition of neutrophil adhesion, chemotaxis, degranulation and superoxide generation, and reduction of edema and pain signals [16].

Isoprostane formation and biological effects

It is well established that lipid peroxidation occurs as a consequence of the formation of free radicals in cells and tissues and represents the most prominent phenomenon of oxidative stress [17]. Isoprostanes, a group of prostaglandin F_2-like compounds, are formed in vitro and in vivo by free radical-catalyzed peroxidation of phospholipid-bound AA. As F_2-isoprostanes are released into the circulation and are less reactive than other lipid peroxidation products, such as lipoperoxides and aldehydes, they can be detected more easily in plasma and urine. At present, F_2-isoprostanes are considered as the most reliable markers of oxidative stress (lipid peroxidation). In addition, they have been shown to have direct biological effects, such as vasoconstriction of the renal glomerular arterioles and stimulation of cell proliferation of vascular smooth muscle cells and endothelial cells [18, 19].

Eicosanoids and diseases

Recent studies using gene knockout mice models for both enzymes and receptors have revealed that eicosanoids play a fundamental role in pathological processes. Imbalance of the major lipid signaling pathways contribute to disease progression and chronic inflammation,

autoimmunity, allergy, cancer, atherosclerosis, metabolic and degenerative diseases.

Eicosanoids in inflammation and sepsis

In the past years, it became evident that eicosanoids can act to both promote and inhibit inflammation. It is accurate to consider these compounds as part of a complex regulatory network that modulates the actions of immune cells and the surrounding microenvironment. Granulocytes, macrophages, neutrophils, platelets, mast cells and endothelial cells are involved in eicosanoid production during inflammation. The quantity and the variety of eicosanoids that are produced during inflammation are determined by the nature and the activation state of the present cells. The impact on immune cells and surrounding stromal cells is mainly determined by the expressed receptors and the intracellular activation pathways to which they are coupled. Vasodilatation and increased permeability of postcapillary venules, representing classical events in the inflammatory response, particularly reflect the effects of COX-2 derived prostaglandins and LTs at sites of inflammation. Particular eicosanoids act as proinflammatory molecules (PGH_2), chemoattractants (LTB_4), platelet aggregation factors (TXA_2), contractor of smooth muscle cells and modifiers of vascular permeability (LTs). PGE_2 and PGI_2 are shown to be potent vasodilatators and are produced in sufficient quantities at inflammatory sites to account for the inflammatory process [20]. To complicate matters, eicosanoids can act as both pro- and anti-inflammatory mediators, depending on the surrounding environment, the existing eicosanoid receptor variants and the duration of inflammation. Certain arachidonate-derived products such as PGE_2 might play protective roles at sites of inflammation by inducing wound healing and resolution. Human peripheral blood mononuclear cells exposed to PGE_2 switched eicosanoid synthesis from predominantly LTB_4 and 5-LO-initiated pathways to synthesis of LXs, a distinct class of LO-derived eicosanoids that act as stop signals of inflammation [21]. Thus, PGE_2 as one of the central prostanoids is represented as more of a modulator rather than a mediator of inflammation. The events in inflammation might be governed by a change of eicosanoid profiles, such that eicosanoids present in the initial phase are gradually replaced by other lipid mediators in the resolution phase.

Scientific knowledge about the complex inflammatory mechanisms of SIRS and sepsis as syndromes characterized by major alterations in inflammatory activity is still lacking. There is evidence that eicosanoids mediate the endotoxin-induced effects; however, the published data are conflicting. Several studies have revealed increased circulating blood levels of COX-derivatives and an increased eicosanoid synthesis has been shown to correlate with severity of sepsis [22]. In contrast to deleterious effects of certain eicosanoids such as TXA_2, other prostanoids such as PGE_1 and PGI_2 have been shown to be more beneficial in endotoxemic or septic shock.

Eicosanoids in atherosclerosis and cardiovascular disease

Several lines of evidence particularly from mouse models implicate an important role of the LOX pathway in atherogenesis. Many processes are involved such as vascular remodeling, synthesis of vasoactive mediators, secretion of growth factors, formation and activity of chemokines, turnover of extracellular matrix compounds, cell death and oxidation of low-density lipoproteins; these contribute to the LOX pathway [23]. LT signaling mediates proliferation and migration of vascular smooth muscle cells and induces endothelial activation; these are critical events in early atherogenesis [24]. Because macrophages represent a major source of 5-LO in the cardiovascular system, LTB_4 has been revealed to play an important role in the accumulation of macrophages at the site of initial foam cell formation [25]. Furthermore, some studies indicate that the LT pathway plays a role in plaque rupture, causing thrombosis and vessel occlusion [26]. Suppression of TXA_2 retards atherogenesis in mice. The COX-2-derived prostanoid PGI_2 appears to be atheroprotective, limiting vascular proliferation, remodeling, hypertension and platelet activation [7]. EETs such as endogenous lipids which are derived through the metabolism of AA by CYP450 epoxygenase enzymes hyperpolarize vascular smooth muscle and induce dilation of coronary arteries and arterioles, and therefore might be endogenous mediators of coronary vasomotion and myocardial perfusion. In addition, EETs have been shown to inhibit vascular smooth muscle migration, decrease inflammation, inhibit platelet aggregation and decrease adhesion molecule expression, and therefore possibly representing an endogenous protective mechanism against atherosclerosis [27].

Isoprostanes such as PG-like compounds derived from the free radical-catalyzed peroxidation of AA have been shown to be increased in association with several atherosclerotic risk factors, including hypercholesterolemia, diabetes mellitus, cigarette smoking and obesity [28]. In addition, there is clinical evidence that F_2-isoprostanes might represent a prognostic marker. Gross et al. revealed a relationship between plasma F_2-isoprostanes and early development of coronary artery calcification [29]. Urinary excretion was found to correlate with several risk factors and was suggested to be an independent risk marker for coronary heart disease [28]. F_2-isoprostanes are discussed further as a pathophysiological biomarker, because they have been shown to be significantly increased in atherosclerotic plaque and to affect vasoconstriction, mitogenesis and monocyte adhesion [30].

Eicosanoids in platelet activation

There is recent evidence for a role of platelets in atherogenesis. Persistent platelet activation as reflected by enhanced excretion of the COX-2 metabolite thromboxane has been reported to accelerate atherogenesis and was associated with increased wall thickness of the carotid artery [31]. Furthermore, high platelet reactivity has been described to be associated with a higher risk for cardiovascular events. Platelet activation is also important in patients with ischemic stroke; increases in thromboxane biosynthesis have been described in the acute phase [32]. In murine models, prostacyclin as an inhibitor of platelet activation has been described to modulate platelet-vascular interactions and to limit the response to thromboxane [33]. In addition, aberrations in the platelet mechanisms in hemostasis constitute the basis for bleeding diathesis. Because eicosanoids play a fundamental role in the activation of platelets, disturbances in eicosanoid metabolism might induce a bleeding tendency. Patients with abnormalities in mobilization of free AA and subsequent transformation to prostaglandins or with deficiencies of cyclooxygenase and thromboxane synthase have been described together with bleeding histories [34].

Eicosanoids in cancer development

Altered AA metabolism in the tumor microenvironment has a profound impact on the pathogenesis of tumor development. The two enzymes, COX-2 and 5-LO, as well as their generated metabolites, have been recognized as essential regulators of cancer development and progression in several tumor types. Most data indicate that PGE_2 is the primary pro-oncogenic prostanoid, stimulating cellular proliferation and angiogenesis, reducing apoptosis, enhancing cellular invasiveness and inhibiting immune surveillance [1]. Another COX-metabolite, implicated in oncogenesis is TXA_2, promoting angiogenesis. A PGD_2 metabolite has recently been described as a potent antitumor agent [35].

Eicosanoids in allergic diseases and asthma

Eicosanoids are well-known mediators of allergic diseases. It has been found that fixation of the allergen on IgE triggers activation of PLA_2 with subsequent liberation and metabolization of AA by COX or LOX pathways. Key mediators including LOX representatives such as LTC_4, LTD_4 and LTE_4, and COX representatives such as PGD_2 and $PGF_{2\alpha}$ do not appear to be immunomodulators but are released from cells during hypersensitivity responses and are responsible for clinical manifestations including bronchial spasms, diarrhea and blood pressure variation [36]. By contrast, lipoxins are shown to counter-regulate the proinflammatory actions of LTs in the pathophysiology of asthma, reflecting a possible role in airway homeostasis [37]. F_2-isoprostanes have been shown to be increased in breath condensates of patients with asthma, indicating that oxidative stress is intimately involved in the pathogenesis of such diseases [38].

Eicosanoids in rheumatic and bone resorptive disease

PGE_2 and LTB_4 are key players in rheumatoid arthritis (RA) as a prototypic inflammatory disease. LTB_4 produced by mononuclear cells seems to be important in orchestrating the induction and perpetuation of inflammation via leukocyte recruitment. PGE_2 is generated by synoviocytes and macrophages and has a proinflammatory role in the progression of RA. By contrast, overproduction of PGE_2 in RA has been shown to have an immunosuppressant effect via activation of lymphocytic suppressor cells. Recently, it has been shown that lipoxins as anti-inflammatory and pro-resolution mediators act in part by reducing neutrophil entry to the inflammation site and stimulating the uptake of apoptotic polymorphonuclear leukocytes by macrophages [39].

PGE_2 is one of the most notable lipid mediators of bone remodeling and has been linked to bone resorptive diseases, inducing osteoclast formation. By contrast, PGE_2 promotes bone formation in vitro by stimulating osteoblastic proliferation and differentiation, showing the multifaceted role of PGE_2 in bone metabolism [40].

Eicosanoids in brain pathologies

Similar to other mammalian cells, eicosanoids are not stored in neural cells but are synthesized rapidly in response to receptor-mediated stimulation. In brain tissue, both neurons and glial cells produce prostanoids, which can be involved in the crosstalk among various neural cells, modulating the neural cell response. Cerebral microvessels and the choroid plexus mainly synthesize thromboxanes. Some prostanoids play an important role in neural activity by modulating the release of hormones and neurotransmitters; others regulate circulatory function and induce trophic effects [41]. At low concentrations, eicosanoids have been shown to protect cortical neurons against glutamate toxicity [42]. Recently, it has been shown that neuronal damage as a result of ischemic injury involves PLA_2 and COX-2, depending on the cell type, time course and type of ischemic insult [43]. In a gene array study, profiling of 12,633 genes in the hippocampal area of patients with Alzheimer dementia indicated an increase in $cPLA_2$ and COX-2 expression, implementing a possible pathogenic role of the COX pathway in neurodegenerative disease [44, 45]. An increased production of F_2-isoprostanes in cerebrospinal fluid has been found in patients with Alzheimer disease and multiple sclerosis, suggesting a possible role as

markers of neuronal oxidative damage [38]. Free radical damage to lipids in brain is discussed as a pathogenic process of neurodegenerative diseases that can be quantified with F_2-isoprostanes [46].

Conclusions

Eicosanoids are lipid signaling molecules that are primarily oxidized from arachidonic acid by enzymatic or non-enzymatic peroxidation. Originally considered as terminal mediators regulating vascular dilation, vascular permeability and platelet aggregation, eicosanoids are actually appreciated playing key roles in the immune response and haven been shown to contribute to formation and progression of many diseases. However, according to the large number of arachidonate metabolites, their diversity of actions and opposing effects and their multiple interaction with other signaling pathways, the clinical significance of these mediators is still inadequately clarified.

A systemic, multiparametric analysis of the eicosanoid pathways in various diseases using tandem mass spectometry could help to improve our understanding of biology and disease pathology. This could implicate new diagnostic and therapeutic strategies.

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