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EICOSANOIDS IN HUMAN PHYSIOLOGY: POLYUNSATURATED FATTY ACID SOURCES, BIOSYNTHESIS, FUNCTIONS, AND THERAPEUTIC IMPLICATIONS

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ABSTRACT

The purpose of this review is to present latest information on the sources, biosynthesis, transport and versatile functions of eicosanoids in human physiology. Eicosanoids, encompassing prostaglandins, thromboxanes, leukotrienes, lipoxins, and their oxygenated derivatives, are lipid mediators derived from C20 polyunsaturated fatty acids, primarily belonging to the omega-6 and omega-3 families. Arachidonic acid, a major precursor, serves as the primary building block for prostaglandins and other eicosanoids. It is stored in cell membrane phospholipids, predominantly in phosphatidylinositol and other complex lipid forms. The release of free arachidonic acid is facilitated by the enzyme phospholipase A2. Eicosanoids exert diverse biological functions within vertebrates, participating in crucial endocrine processes such as inflammation, reproduction, gastric secretion, and blood pressure regulation. They contribute to homeostasis maintenance by modulating vascular permeability, safeguarding gastric mucosal integrity, and regulating platelet aggregation. Notably, eicosanoids exhibit both pro-inflammatory and anti-inflammatory properties, engaging in complex regulatory networks involving immune cells and the microenvironment. They also play significant roles in neural cell crosstalk, atherosclerosis, cancer development, platelet activation, and allergic/asthmatic diseases. Understanding the intricate mechanisms and interactions of eicosanoids holds great potential for targeted therapeutic interventions. Further research in this field can provide valuable insights into their precise roles and aid in the development of novel treatments for a wide range of diseases.

Keywords*:* Eicosanoids, Biosynthesis, Functions, Human physiology, Lipid mediators

İNSAN FİZYOLOJİSİNDE EİKOZANOİDLER: ÇOKLU DOYMAMIŞ YAĞ ASİDİ KAYNAKLARI, BİYOSENTEZ, FONKSİYONLAR VE TEDAVİ İLİŞKİLERİ

ÖZET

Bu incelemenin amacı, insan fizyolojisinde eikozanoidlerin kaynakları, biyosentezi, taşınması ve çok yönlü işlevleri hakkında en güncel bilgiyi sunmaktır. Prostaglandinler, tromboksanlar, lökotrienler, lipoksinler ve oksijenli türevleri gibi eikozanoidler, temel olarak omega-6 ve omega-3 ailelerine ait C20 çoklu doymamış yağ asitlerinden türeyen lipit aracılarıdır. Ana öncü olan araşidonik asit, prostaglandinler ve diğer eikozanoidler için temel yapı taşı olarak hizmet eder. Hücre membran fosfolipitlerinde, özellikle fosfatidilinositol ve diğer kompleks lipid formlarında depolanır. Serbest araşidonik asidin salınımı, enzim fosfolipaz A2 tarafından kolaylaştırılır. Eikozanoidler omurgalılarda çeşitli biyolojik işlevler göstererek, inflamasyon, üreme, gastrik salgı ve kan basıncı düzenlemesi gibi önemli endokrin süreçlere katılırlar. Vasküler geçirgenliği düzenleyerek homeostazın korunmasına katkıda bulunurlar, gastrik mukozal bütünlüğü korurlar ve trombosit agregasyonunu düzenlerler. Özellikle, eikozanoidler hem pro-inflamatuar hem de anti-inflamatuar özelliklere sahiptir, bağışıklık hücreleri ve mikroçevre ile ilişkili karmaşık düzenleme ağlarında yer alırlar. Ayrıca, sinir hücreleri arasındaki etkileşimlerde, aterosklerozda, kanser gelişiminde, trombosit aktivasyonunda ve allerjik/astmatik hastalıklarda önemli roller üstlenirler. Eikozanoidlerin karmaşık mekanizmalarını ve etkileşimlerini anlamak, hedefe yönelik terapötik müdahaleler için büyük potansiyele sahiptir. Bu alandaki daha fazla araştırma, kesin rollerini anlamamıza ve geniş bir hastalık yelpazesi için yeni tedavilerin geliştirilmesine yardımcı olabilir.

Anahtar kelimeler: Eikozanoidler, Biyosentez, İşlevler, İnsan fizyolojisi, Lipit aracılar

1. INTRODUCTION

In the context of cellular and nuclear membranes, eicosanoids, a group of bioactive molecules, are synthesized as needed rather than being stored within cells. These molecules are derived from the fatty acids present in these membranes, which are released and subsequently metabolized to generate a diverse array of eicosanoids. The most commonly encountered polyunsaturated fatty acid in eicosanoid synthesis is arachidonic acid, consisting of 20 carbon atoms, as reflected by the Greek term 'eicosa' meaning '20 carbon.' Notable examples of eicosanoids include prostaglandins, thromboxanes, leukotrienes, and lipoxins. Functioning predominantly on cells of their own production or neighboring cells, these molecules act over short distances and time frames, classifying them as autocrine/paracrine hormones. With wide distribution across various cells and tissues in the body, eicosanoids exert diverse biological actions, particularly playing critical roles in endocrine systems systems (1–6). In mammals, the biosynthesis and structural properties of eicosanoids are well understood. These molecules are not stored but are synthesized in response to hormonal stimulation or mechanical trauma in all mammalian tissues, acting as paracrine or autocrine modulators (5,7). Their actions are mediated through the activation of membrane receptors (1,5).

The goal of this study is to gain a comprehensive understanding of the biosynthesis, functions, and molecular mechanisms of eicosanoids, with a focus on the involvement of arachidonic acid in prostaglandin production.

2. EICOSANOIDS

2.1. Biosynthesis and Phospholipase A2

Mechanical trauma, ischemia, physical perturbations, pathogen attacks, or various stimuli originating from neighboring cells, tissues, or pathogens, such as chemotactic factors, cytokines, growth factors, and certain eicosanoids, serve as triggers for eicosanoid biosynthesis. In response to these stimuli, activated cells release a group of enzymes called phospholipase A2s (PLA2s), which play a vital role in releasing ω6 and ω3 fatty acids from membrane phospholipid storage. Specifically, these fatty acids are ester-linked to the SN2 position of membrane phospholipids, and PLA2s function as esterases to facilitate their release. PLA2s encompass multiple classes, among which the cytosolic type IV PLA2s (cPLA2s) appear to be primarily responsible for fatty acid release during various cellular activation processes. It is worth noting that cPLA2s selectively bind to phospholipids harboring arachidonic acid (AA), eicosapentaenoic acid (EPA), or glycerophospholipid-A (GPLA) at the SN2 position. Additionally, cPLA2 may also generate lysophospholipids, which can act as platelet-activating factors (5,6,8,9).

2.2. Polyunsaturated Fatty Acid Sources and Classes

Eicosanoids are oxygen-containing products derived from straight-chain polyunsaturated fatty acids (PUFAs) with a carbon chain length of 20. These PUFAs serve as precursors for the synthesis of eicosanoids, and they include:

a. Arachidonic acid (C20:4n6 - AA): Arachidonic acid is an ω6 fatty acid with four cis double bonds located between carbons 5-6, 8-9, 11-12, and 14-15.

b. Adrenic acid (C22:4n6 - ADA): Adrenic acid is an ω6 fatty acid with four cis double bonds located between carbons 7-8, 10-11, 13-14, and 17-18.

c. Eicosapentaenoic acid (C20:5n3 - EPA): Eicosapentaenoic acid is an ω-3 fatty acid with five cis double bonds located between carbons 5-6, 8-9, 11-12, 14-15, and 17-18.

d. Dihomo-gamma-linolenic acid (C20:3n6 - DGLA): Dihomo-gamma-linolenic acid is an ω6 fatty acid with three cis double bonds located between carbons 8-9, 11-12, and 14-15.
e. Mead acid (C20:3n9): Mead acid is an ω9 fatty acid containing three cis double bonds located between carbons 5-6, 8-9, and 11-12.

Arachidonic acid gives rise to ω6 series eicosanoids, which include leukotrienes (LT) such as LTA4, LTB4, LTC4, LTD4, and LTE4; eoxins (EX) such as EXA4, EXC4, EXD4, and EXE4; prostaglandins (PG) such as PGG2, PGH2, PGE2, PGD2, PGF2 alpha, PGA2, and PGB2; thromboxanes (TX) such as TXA2 and TXB2; and hydroxyeicosatetraenoic acids (HETE) such as 5-HETE, 12-HETE, 15-HETE, 20-HETE, and 19-HETE (7,10–14). Eicosanoids derived from dihomo-gamma-linolenic acid series are structural analogues of arachidonic acid-derived eicosanoids but differ in having one fewer double bond (between carbons 5 and 6). Examples of these analogues include PGA1, PGE1, and TXA1. Eicosanoid refers to straight-chain polyunsaturated fatty acids (PUFAs) with 20 carbon units in length that have been metabolized or otherwise converted to oxygen-containing products. The PUFA precursors to eicosanoids include (7,10–14).

Prostaglandins (PGs): Prostaglandins (PGs) are a diverse group of hormone-like substances that are primarily synthesized within the prostate gland and exert localized effects in nearby tissues. These bioactive molecules play a multifaceted role in numerous physiological processes, showcasing their wide-ranging influence within the body. One of the prominent functions of prostaglandins is their involvement in the regulation of smooth muscle contractions, particularly in the uterus. During menstruation, prostaglandins facilitate the contraction of uterine muscles, aiding in the shedding of the uterine lining. Additionally, prostaglandins are instrumental in inducing labor contractions during childbirth. Prostaglandins also exert regulatory control over blood flow to specific organs. They can cause vasoconstriction or vasodilation, depending on the specific prostaglandin type and the target tissue. By modulating blood vessel diameter, prostaglandins play a crucial role in maintaining proper blood pressure and ensuring adequate perfusion to vital organs. Inflammation, a complex immune response, is another arena where prostaglandins exert their influence. They contribute to the initiation and propagation of inflammatory processes, promoting the migration of immune cells to the site of injury or infection. Prostaglandins are involved in the regulation of vasodilation and vascular permeability, facilitating the influx of immune cells and the release of inflammatory mediators. Prostaglandins also impact various physiological functions, including body temperature regulation, pain perception, and the sleep-wake cycle. They can

influence the hypothalamus, the body's temperature control center, leading to fever or heat dissipation. Additionally, prostaglandins contribute to the sensitization of pain receptors, enhancing pain perception. In the context of the sleep-wake cycle, prostaglandins interact with other neurochemicals to regulate sleep onset and maintenance (2,4,5).

Thromboxanes (TXs): Thromboxanes (TXs) are biologically active compounds characterized by the presence of ether-containing 6-membered rings. These molecules are primarily synthesized from platelets, also known as thrombocytes. Thromboxanes play a crucial role in the regulation of blood clotting processes and the modulation of blood flow dynamics in relation to clot formation. One of the key functions of thromboxanes is their ability to promote platelet aggregation, leading to the formation of blood clots, a vital mechanism in preventing excessive bleeding and promoting wound healing. Thromboxanes also contribute to the constriction of blood vessels, particularly in the vicinity of a clot, resulting in a decrease in blood flow to the clot site. In addition to their role in hemostasis, thromboxanes are involved in various physiological and pathological processes. They participate in the regulation of inflammation, immune responses, and the modulation of vascular tone. Furthermore, thromboxanes have been implicated in the pathogenesis of cardiovascular diseases, such as hypertension and atherosclerosis (1,2,5,6).

Leukotrienes (LTs): Leukotrienes, a group of bioactive lipid mediators, are primarily synthesized within leukocytes, specifically in cells such as mast cells, basophils, and eosinophils. These molecules are characterized by the presence of three conjugated double bonds, which confer unique biological activities and signaling capabilities. One notable leukotriene, leukotriene D4 (LTD4), exerts a powerful effect on smooth muscle contraction in the airways of the lungs. Upon its release, LTD4 acts as a potent bronchoconstrictor, leading to the narrowing of the airway passages. This constriction of the airways can trigger asthmatic attacks and respiratory distress, particularly in individuals with heightened leukotriene production or increased sensitivity to these mediators. Leukotrienes are known to play a significant role in various inflammatory and immune responses. They contribute to the recruitment and activation of immune cells, promote the release of pro-inflammatory cytokines, and regulate vascular permeability. Additionally, leukotrienes are involved in the modulation of blood flow, the regulation of smooth muscle tone, and the initiation and perpetuation of inflammatory processes. In certain pathological conditions, such as asthma and allergic reactions, there is an upregulation of leukotriene production, leading to heightened inflammatory responses and bronchoconstriction. Consequently, blocking the actions of

leukotrienes or inhibiting their synthesis has become a target for therapeutic interventions aimed at managing asthma and related respiratory disorders (2,4,6,15).

Lipoxins (LXs): Lipoxins (LXs) are a class of eicosanoids that are formed through interactions involving lipoxygenase enzymes. These bioactive lipid mediators are structurally similar to leukotrienes but possess distinct characteristics, particularly the presence of multiple hydroxyl groups along their linear chain. One prominent feature of lipoxins is their ability to exhibit potent anti-inflammatory effects. They function as endogenous "braking signals" in inflammatory responses, playing a crucial role in resolving inflammation and promoting tissue homeostasis. Lipoxins act by inhibiting the recruitment and activation of immune cells, suppressing the release of pro-inflammatory molecules, and promoting the clearance of inflammatory mediators. Interestingly, the production of lipoxins can be influenced by the administration of aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs). Aspirin, in particular, can enhance the generation of lipoxins by altering the enzymatic activities involved in their synthesis. This unique interaction between aspirin and lipoxins further contributes to the anti-inflammatory properties of aspirin and highlights the complex interplay between eicosanoids and pharmacological interventions. In addition to their anti-inflammatory actions, lipoxins have been implicated in various physiological processes, such as the regulation of vascular tone, platelet aggregation, and tissue repair. They also interact with other lipid mediators and immune molecules to orchestrate intricate signalling networks involved in inflammation resolution and immune regulation (1,2,6).

2.3. Pathways: Cyclooxygenase, Lipoxygenase, Cytochrome Epoxygenase

Eicosanoid biosynthesis involves multiple enzymatic pathways, with several rate-limiting steps and selective mechanisms for arachidonate incorporation into phospholipids. The process begins with the activation of phospholipase A2, which leads to the release of arachidonic acid from membrane phospholipids in response to various physiological and pathological factors, including hormones and cytokines. This step is crucial for the subsequent production of eicosanoids. There are three main enzymatic pathways involved in eicosanoid formation: cyclooxygenases (COXs), lipoxygenases (LOXs), and cytochrome P-450 epoxygenases (CYPs). Additionally, the CYPs also play a role in the oxidation of sterols and bile acids. Among these pathways, the COX pathway, which consists of two isoforms, COX-1 and COX-2, is responsible for generating prostaglandins PGG2 and PGH2. These intermediates

are further converted by specific synthases into various prostaglandins, prostacyclin, and thromboxanes (TXs). The specific enzymes and synthases involved in each pathway determine the type and function of the eicosanoids produced. The diverse range of eicosanoids generated through these pathways allows for a wide array of physiological responses and regulatory mechanisms in the body. Understanding the intricacies of eicosanoid biosynthesis pathways is essential for comprehending their role in health and disease, as well as for developing targeted therapeutic interventions (1,6,7,16).

The initial and crucial step in eicosanoid biosynthesis is the liberation of polyunsaturated (C20) fatty acids from membrane phospholipids. Arachidonic acid, the most prevalent precursor of eicosanoids, undergoes precise regulation through several types of phospholipase A2 or phospholipase C enzymes, along with subsequent mono- and diacylglycerol lipases (17). Following its release, arachidonic acid undergoes enzymatic conversion into various eicosanoids through three primary pathways: cyclooxygenase, lipoxygenase, and cytochrome P-450 epoxygenase (7). These pathways dictate the specific types and functions of the eicosanoids produced, playing significant roles in various physiological and pathological processes. Understanding the regulation and enzymatic conversion of arachidonic acid is crucial for comprehending the intricate network of eicosanoid biosynthesis and its implications in health and disease.

The Cyclooxygenase (COX) pathway: This pathway is responsible for the synthesis of prostanoids, including prostaglandins, thromboxanes, and prostacyclin. Two major enzymes, COX-1 and COX-2, initiate the production of prostaglandins. COX-1 is constitutively expressed, while COX-2 is induced by various factors. Arachidonic acid is converted to prostaglandin H2 (PGH2) by COX enzymes, and tissue-specific prostanoids are formed through subsequent reactions involving isomerases and synthases (12). For instance, thromboxane A2 (TXA2) synthase is found in platelets and macrophages, prostaglandin I2 (PGI2) synthase is present in endothelial cells, and prostaglandin F2 (PGF2) synthase is abundant in the uterus (5,18). The cyclooxygenase pathway produces eicosanoids with ring structures and plays a crucial role in physiological cellular functions as well as inflammation and chronic diseases (5,7).

The Lipoxygenase (LOX) pathway: It is responsible for the production of leukotrienes. Inflammatory cells initiate the synthesis of leukotrienes, which are members of the LT family of lipid mediators. Arachidonic acid is converted to hydroperoxyl eicosatetraenoic acid (HPETE) by the enzyme 5-lipoxygenase (5-LOX), with the assistance of five-lipoxygenase

activating protein (FLAP). Most HPETE molecules are converted to leukotriene A4 (LTA4), which can serve as a precursor for lipoxins or undergo further transformation routes (5,19). The lipoxygenase pathway produces leukotrienes and lipoxins, and it plays a significant role in inflammation. Anti-leukotriene medications are used for the treatment of asthma (5,7).

The cytochrome P450 epoxygenase pathway: It catalyzes the monooxygenation of arachidonic acid and primarily produces epoxy-eicosatrienoic acids (EETs). However, hydroxylases can also convert arachidonic acid to hydroxy-eicosatetraenoic acids (HETEs). The cytochrome P450 epoxygenase pathway is involved in the metabolism of arachidonic acid and contributes to the regulation of various physiological processes (5,7).

Understanding the different pathways of eicosanoid biosynthesis provides insights into their diverse functions and their involvement in normal physiology, inflammation, and disease conditions. The interplay between these pathways and the regulation of enzymatic conversions determine the specific types of eicosanoids produced and their biological effects.

2.4. Transportation in Tissues

The transport of eicosanoids across cell membranes is not a passive process due to their lipid nature. Efflux transporters, such as multidrug-resistance proteins (MRPs), play a crucial role in transporting newly synthesized eicosanoids out of the cells responsible for their production. These transporters facilitate the export of eicosanoids from the intracellular environment to the extracellular space. On the other hand, the uptake of eicosanoids into cells is regulated by organic anion transporter proteins. These proteins facilitate the internalization of eicosanoids, allowing them to exert their biological effects within the cell. The interplay between efflux transporters and uptake transporters ensures the dynamic movement of eicosanoids between the intracellular and extracellular compartments. The abundance and distribution of eicosanoid receptors and transporters in different tissues play a crucial role in determining the localized effects of these bioactive lipid mediators. Eicosanoids are thought to act as local or paracrine effectors, meaning they exert their specific biochemical actions within close proximity to their site of synthesis. This localized action allows eicosanoids to initiate specific biochemical reactions in specific tissues, contributing to the regulation of various physiological processes (5,6).

2.5. Functions in Human Physiology

Eicosanoids, with their diverse array of functions, play critical roles in various physiological and pathological processes within the human body. These bioactive lipid mediators exhibit a wide range of activities, including but not limited to inflammation regulation, immune response modulation, allergy and hypersensitivity reactions, fever induction, and pain perception. In the context of inflammation, eicosanoids act as key mediators, promoting or inhibiting the inflammatory response depending on the specific circumstances. They regulate the recruitment and activation of immune cells, the release of inflammatory mediators, and the modulation of vascular permeability. Eicosanoids contribute to the initiation, amplification, and resolution of inflammatory processes, helping to restore tissue homeostasis. During pregnancy and childbirth, eicosanoids are involved in the regulation of uterine contraction and relaxation, contributing to the coordination and timing of labor. Prostaglandins, in particular, play a crucial role in initiating and maintaining uterine contractions, while also influencing cervical ripening and the rupture of fetal membranes. Pain perception is another area where eicosanoids exert their influence. These lipid mediators can sensitize pain receptors, leading to heightened pain sensitivity and perception. Additionally, eicosanoids contribute to the development of chronic pain conditions and can modulate the efficacy of analgesic medications. Eicosanoids also participate in the regulation of cell growth and proliferation, influencing processes such as cell division, differentiation, and apoptosis. They play a role in the control of blood pressure by modulating vascular tone and renal function. Eicosanoids are involved in the regulation of regional blood flow to different tissues, ensuring appropriate perfusion and oxygenation of vital organs. In terms of signaling, eicosanoids primarily function as autocrine and paracrine agents. They act locally within their cells of origin or in close proximity to exert their effects on neighboring cells. However, some eicosanoids can also act as endocrine agents, traveling through the bloodstream to regulate the activity of distant cells and tissues (1,20).

2.5.1. Inflammation and Sepsis

In recent years, it has become increasingly evident that eicosanoids play a dual role in the regulation of inflammation, with the ability to both promote and inhibit this complex biological process. Rather than acting in isolation, eicosanoids should be recognized as integral components of a sophisticated regulatory network that modulates the activities of immune cells

and their interactions with the surrounding microenvironment. During an inflammatory response, various cell types including granulocytes, macrophages, neutrophils, platelets, mast cells, and endothelial cells actively produce eicosanoids. The specific characteristics and activation states of these cells determine the specific types and quantities of eicosanoids generated during inflammation. Furthermore, the expressed receptors on these cells and the intracellular signaling pathways to which they are linked exert significant influence on the behavior of immune cells as well as the surrounding stromal cells. Classic inflammatory responses, such as vasodilation and increased permeability of postcapillary venules, reflect the effects of eicosanoids derived from the cyclooxygenase-2 (COX-2) pathway, namely prostaglandins and leukotrienes. These bioactive molecules contribute to the recruitment of immune cells to the site of inflammation and facilitate the delivery of essential immune mediators. The intricate interplay between pro-inflammatory and anti-inflammatory eicosanoids is crucial for maintaining a balanced immune response and promoting the resolution of inflammation. Understanding the precise roles and mechanisms by which eicosanoids modulate inflammation is of utmost importance, particularly in the context of sepsis, a severe condition characterized by a dysregulated host response to infection. In sepsis, dysregulated production and imbalance of eicosanoids can exacerbate systemic inflammation, impair vascular integrity, and contribute to organ dysfunction. Therefore, unraveling the complexities of eicosanoid-mediated immune regulation holds great potential for the development of targeted therapeutic approaches in the management of inflammatory disorders and sepsis (1,6,20,21).

2.5.2. Brain Diseases

Eicosanoids, a diverse group of lipid mediators, exhibit dynamic synthesis and play crucial roles in the central nervous system. Unlike some molecules that are stored within neural cells, eicosanoids are rapidly produced in response to receptor-mediated stimulation. Within the intricate network of brain tissue, both neurons and glial cells actively synthesize prostanoids, a subclass of eicosanoids, which participate in intricate neural cell crosstalk and modulate the response of neural cells. Notably, thromboxanes, another class of eicosanoids, are primarily synthesized by cerebral microvessels and the choroid plexus, contributing to the regulation of cerebrovascular function. The effects of eicosanoids on neural activity are diverse and multifaceted. Some prostanoids act as modulators of hormone and neurotransmitter release,

exerting a direct influence on neural signaling. Others play a crucial role in regulating circulatory function within the brain and induce trophic effects, supporting the growth and survival of neural cells. Additionally, eicosanoids have been shown to exhibit neuroprotective properties, specifically safeguarding cortical neurons against glutamate-induced toxicity, even at low concentrations. These findings underscore the intricate and multifunctional roles of eicosanoids in neural physiology and emphasize their significance in maintaining brain homeostasis (1,13,22).

2.5.3. Atherosclerosis and Cardiovascular Disease

Mounting evidence, particularly from studies conducted on mouse models, has highlighted the significant involvement of the lipoxygenase (LOX) pathway in atherosclerosis, a major contributor to cardiovascular disease. Multiple processes contribute to atherogenesis, and the LOX pathway plays a crucial role in each of these processes. These include 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. LT signaling, mediated by products of the LOX pathway, promotes the proliferation and migration of vascular smooth muscle cells and activates the endothelium, both of which are key events in the early stages of atherosclerosis. Notably, LTB4, a specific product of the LOX pathway, has been shown to play a pivotal role in the accumulation of macrophages at the site of initial foam cell formation, as macrophages are a major source of 5-lipoxygenase (5-LO) in the cardiovascular system. These findings underscore the intricate involvement of eicosanoids, particularly those generated via the LOX pathway, in the pathogenesis of atherosclerosis and cardiovascular disease (1,23,24).

2.5.4. Rheumatoid Arthritis and Bone Resorption Disease

Eicosanoids, particularly PGE2 and LTB4, play significant roles in the pathogenesis of rheumatoid arthritis (RA), a prototypic inflammatory disease. LTB4, produced by mononuclear cells, is involved in orchestrating the initiation and maintenance of inflammation by facilitating leukocyte recruitment. Synoviocytes and macrophages, on the other hand, produce PGE2, which contributes to the proinflammatory processes associated with the progression of RA. Interestingly, in RA, the overproduction of PGE2 has been found to have an

immunosuppressive effect through the activation of lymphocytic suppressor cells. In recent studies, lipoxins have emerged as important mediators with anti-inflammatory and pro-resolution properties. Lipoxins have been shown to decrease neutrophil entry to the site of inflammation and promote macrophage uptake of apoptotic polymorphonuclear leukocytes, thereby promoting resolution of inflammation. These findings shed light on the intricate involvement of eicosanoids in the pathogenesis of rheumatoid arthritis and provide potential targets for therapeutic interventions (1,25–27).

2.5.5. Cancer Development

The dysregulation of arachidonic acid (AA) metabolism within the tumor microenvironment has profound implications for cancer pathogenesis. Enzymes such as COX-2 and 5-LO, along with their metabolites, have been identified as crucial regulators of cancer development and progression across various types of tumors. Among the eicosanoids, prostaglandin E2 (PGE2) has emerged as a primary pro-oncogenic prostanoid. PGE2 promotes cellular proliferation and angiogenesis, inhibits apoptosis, enhances cellular invasiveness, and suppresses immune surveillance, as supported by a wealth of data. Thromboxane A2 (TXA2), another metabolite of COX, promotes angiogenesis and has been implicated in oncogenesis. Conversely, a metabolite of prostaglandin D2 (PGD2) was recently discovered to possess potent anti-tumor properties, adding complexity to the role of eicosanoids in cancer biology. These findings highlight the intricate involvement of eicosanoids in cancer development and provide potential avenues for therapeutic intervention (1,21,28,29).

2.5.6. Platelet Activation

Emerging evidence suggests that platelets play a significant role in atherogenesis, the process of plaque formation in arteries. Persistent platelet activation, as indicated by increased thromboxane excretion—a metabolite of COX-2—has been associated with accelerated atherogenesis and increased carotid artery wall thickness. Moreover, heightened platelet reactivity has been linked to an elevated risk of cardiovascular events. These observations underscore the involvement of eicosanoids in platelet activation and their contribution to cardiovascular disease pathology (1,30,31).

2.5.7. Allergic and Asthmatic Diseases

Eicosanoids have long been recognized as mediators of allergic diseases. The process of allergen binding to immunoglobulin E (IgE) triggers the activation of phospholipase A2 (PLA2), leading to the liberation and subsequent metabolism of arachidonic acid (AA) via the COX or LOX pathways. Key mediators, including leukotrienes (LTC4, LTD4, LTE4) from the LOX pathway, and prostaglandins (PGD2, PGF2a) from the COX pathway, are not direct immunomodulators but are released by cells during hypersensitivity responses. These eicosanoids are responsible for various clinical manifestations such as bronchial spasms, diarrhea, and blood pressure fluctuations observed in allergic and asthmatic diseases (1,15,32).

3. DISCUSSION AND CONCLUSION

Eicosanoids play diverse and intricate roles in numerous physiological and pathological processes within the human body. These lipid mediators are rapidly synthesized in response to various stimuli and act as part of complex regulatory networks. Eicosanoids exhibit both pro-inflammatory and anti-inflammatory properties, contributing to the modulation of immune cell actions and the microenvironment in inflammation and sepsis. Furthermore, they are involved in neural cell communication, influencing neural cell responses in brain tissue. In atherosclerosis and cardiovascular disease, eicosanoids have been implicated in vascular remodelling, vasoactive mediator synthesis, and cellular processes associated with disease progression. In rheumatoid arthritis and bone resorption diseases, eicosanoids contribute to the initiation and maintenance of inflammation, influencing immune responses and tissue damage. Additionally, eicosanoids play significant roles in cancer development, with specific metabolites promoting tumour growth and progression. Platelet activation and allergic/asthmatic diseases also involve eicosanoid-mediated mechanisms that impact cardiovascular health and hypersensitivity responses, respectively.

Understanding the multifaceted functions of eicosanoids is crucial for developing targeted therapeutic approaches. Further research into their precise mechanisms of action and the interactions between different eicosanoids will enhance our knowledge of these lipid mediators and potentially lead to the development of novel treatments for various diseases.

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Fig 1. Depiction of the structures of some key eicosanoids. The figure provides visual representations of these eicosanoids, showcasing their distinctive molecular structures (2).