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Biosynthesis and action of eicosanoids in the inflammatory process

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Abstract
Eicosanoids are hormones derived from polyunsaturated fatty acids, and are responsible for regulating the immune response, especially in the inflammatory process and in autoimmune diseases. Such substances may have a highly inflammatory nature and are triggered by their level of concentration in the body, which leads to the development of cardiovascular diseases, cancer, neuroinflammation and anaphylaxis. Enzymes that are part of the metabolic process are the main targets of anti-inflammatory drugs. The present research aimed to investigate the metabolism of the main eicosanoids that act on the inflammatory response and characterize the polyunsaturated fatty acids that constitute the profile of these hormones. This study addresses the current understanding of the metabolism of eicosanoids and may contribute to the discovery of new biopharmaceuticals and consolidation of the knowledge on the pathophysiological process of inflammatory diseases.
Key Word*: Prostaglandins; Lipids; Inflammation. Metabolism. Health.*
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I. Introduction

Lipids contribute to the formation of eicosanoids, lipoproteins, phospholipids, ketone bodies and triglycerides, and the product of their breakdown, fatty acids, are precursors of metabolic pathways that ensure the functioning of the metabolism [47,51].

Eicosanoids are hormones that have a paracrine action, i.e., they are short-distance messengers and act only in cells close to those in which they are synthesized [64]. They are derivatives of essential fatty acids, which are lipids with a polyunsaturated chain, and can be obtained through the diet, since the mammalian metabolism is not able to introduce unsaturations beyond carbon 9, thus making the endogenous biosynthesis of these molecules impossible [41]. Such substances are found mainly in grains and fish oils [39].

The classification of eicosanoids is represented by the following distinct classes: leukotrienes, lipoxins, prostacyclines, prostaglandins and thromboxanes. These substances can act together or separately and have an important role in the inflammatory response, especially in the last three classes mentioned, which are originated by the cyclooxygenase pathway [14].

The beginning of the metabolic pathway that involves the production of inflammatory messengers is based on two enzymes, i.e., cyclooxygenases (COX), which consist of three isoenzymes, COX-1, COX-2 and COX-3; the first two of which frequently act in the tissues of the human organism[5]. Lipoxygenases (LOX) act mildly in the inflammatory process compared to COX, and have 5HPETE as main enzyme of the metabolic pathway[7].

In order for the action of enzymes that participate in the pathway of eicosanoid metabolism to occur, the substrates, such as arachidonic acid, which trigger the inflammation process, are necessary [13]. Therefore, the main mechanisms of action of anti-inflammatory drugs involve the inhibition of the activity of enzymes that participate in the process of metabolizing substrates that generate inflammatory compounds at certain times in the metabolic pathway[19,49].

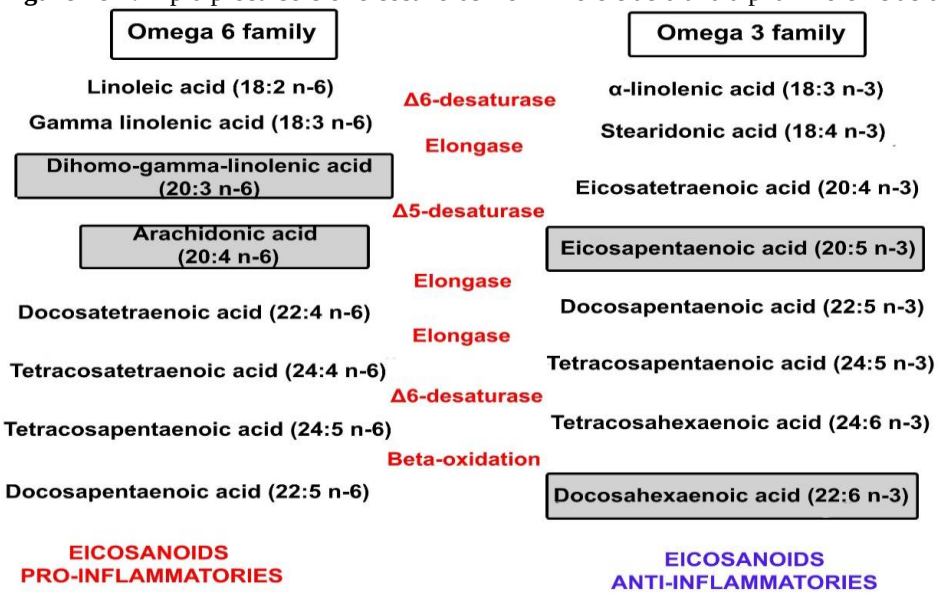
Knowledge about the metabolism of eicosanoids helps in the understanding of pharmacology and has aroused the interest of the scientific community in regards to the discovery of bioactive substances from natural products[67, 68]. This research is a review of the literature and has the aim of investigating the metabolism of the main eicosanoids that act on the inflammatory response and characterizing the polyunsaturated fatty acids that constitute the profile of these inflammatory mediators.

Biosynthesis of eicosanoids

Eicosanoids are derived from polyunsaturated fatty acids that have a carbon chain ≥ 20, these being arachidonic acid (AA 20:4 n-6), dihomo-gamma-linolenic acid (DGLA 20:3 n-6), eicosapentaenoic acid (EPA 20:5 n-3) and docosahexaenoic acid (DHA 22: 6 n-3), the main precursor lipids of biosynthesis[4]. However, such

fatty acids are metabolites of other lipids, the representatives of the omega 3 and 6 families, alpha-linolenic acid (ALA 18:3 n-3) and linoleic acid (LA 18:2 n-6) respectively[29]. Figure 1 demonstrates the biosynthesis of eicosanoids derived from polyunsaturated fatty acids. The main enzymes that are part of this process are desaturases, which have the function of inserting unsaturations between carbons, and elongases, which increase the size of the carbon chain[27].

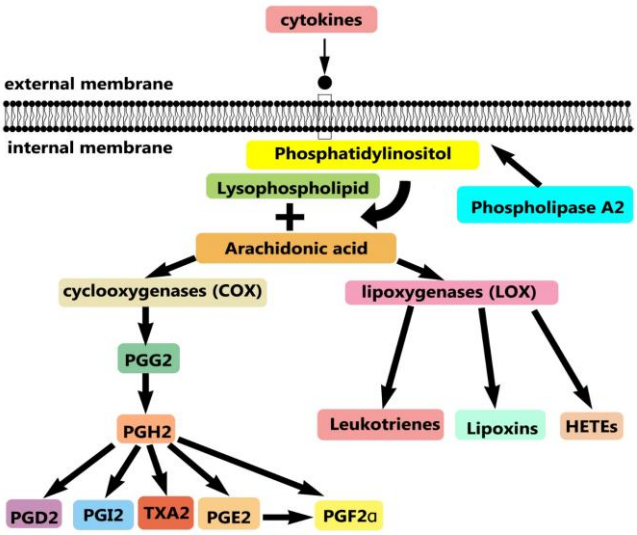
Figure no 1: Lipid precursors of eicosanoids from linoleic acid and alpha-linolenic acid.



Eicosanoids biosynthesized from omega 6 fatty acids are considered pro-inflammatory, while the consumption of omega 3 lipids is interesting for promoting homeostasis since they are considered anti-inflammatory[60]. The effect of n-3 was tested on cardiomyotic apoptosis caused by sepsis and it was found that these fatty acids attenuated the production of pro-inflammatory cytokines, thus contributing to the inhibition of myocardial lesions[55].

For the biosynthesis of eicosanoids to occur, the cleavage of polyunsaturated fatty acids from membrane phospholipids is necessary[8]. Figure 2 shows that when AA is formed from LA, most of the eicosanoids are biosynthesized, i.e., prostanoids, leukotrienes and lipoxins, and hydroxyeicosatetraenoic acid-HETEs, through the enzymes cyclooxygenases or lipoxygenases[35]. The oxidation products of AA by the COX-2 pathway, an enzyme induced by inflammatory stimuli, catalyzes the biosynthesis of prostanoids after the formation of the common precursor, prostaglandin H2[45].

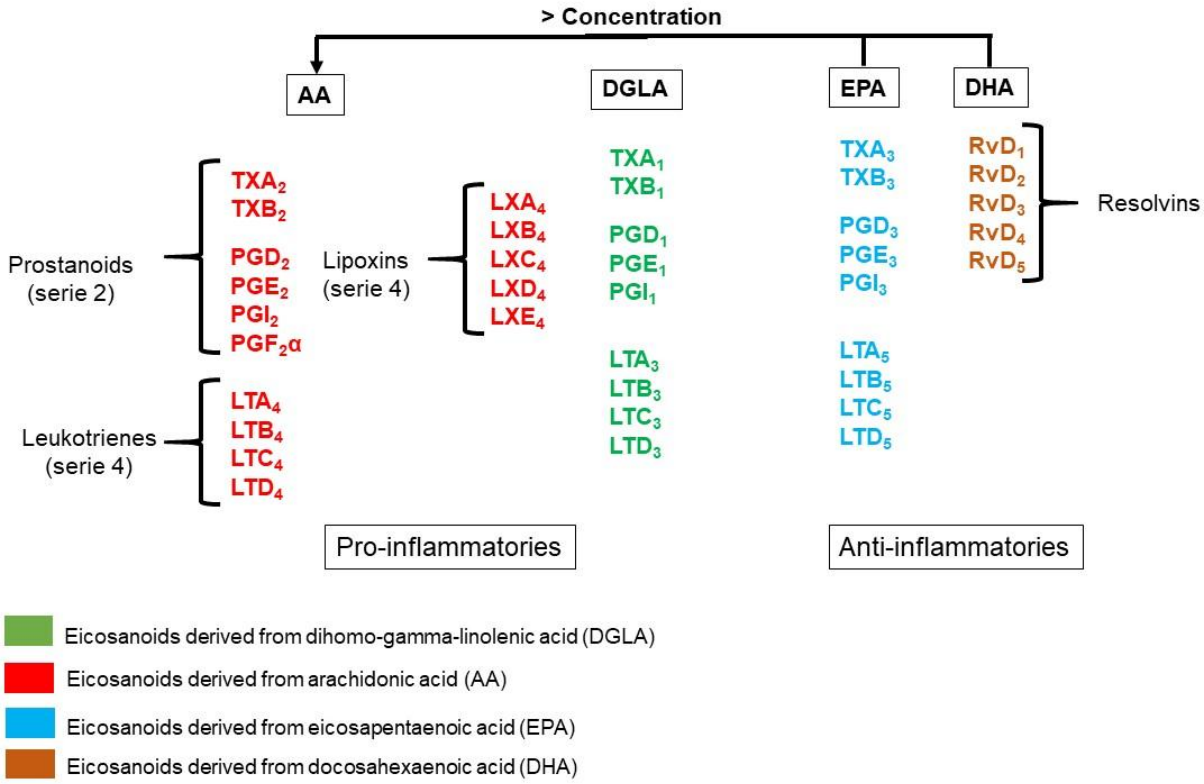
Figure no 2: Biosynthesis of eicosanoids formed from the release of arachidonic acid by the cyclooxygenase pathway.



Arachidonic acid is the most frequently used substrate in scientific research due to the amount of pro-inflammatory compounds produced by its oxidation, and the COX-1/2 pathway is the main target of drugs with anti-inflammatory potential[37,48]. In Figure 2, it can be seen that such a substrate can be released into the cytosol through the hydrolysis of glycerophospholipids of membranes, i.e., when tissue injury occurs[7]. This reaction is catalyzed by the phospholipase A2/C class of enzymes, which is stimulated by chemical messengers that will bind to the cellular receptor, promoting, for example, the action of phospholipase A2 with the formation of lysophospholipid and polyunsaturated fatty acid [8]. Then, the formation of eicosanoids occurs through the enzymes cyclooxygenases or lipoxygenases [12,15,17].

Eicosanoids can be divided into groups, the main one of scientific interest being prostanoids, which consist of prostaglandins (PGs), thromboxanes (TXs) and prostacyclines (PGI)[31,65]. These are found in all organs, and those of series 2 are the main pro-inflammatory compounds and are produced by the precursor AA, as shown in Figure 3. EPA produces series 3 prostanoids and series 5 leukotrienes, while DGLA produces series 1 prostanoids and series 3 leukotrienes. DHA assists in the biosynthesis of LOX pathway hormones[60,62].

Figure no 3: Polyunsaturated fatty acid substrates in the biosynthesis of eicosanoids.



The increase in the polyunsaturated fatty acids EPA and DHA exerts an anti-inflammatory effect and causes the reduction of series 2 eicosanoids due to the unavailability of the AA substrate. Therefore, the ratio of such lipids is important in that it indicates the level of inflammation in certain pathologies, for example, in stroke[30].

The importance of pro-inflammatory prostanoids does not only refer to the inflammation process since these substances are bioactive lipid mediators and exert both a physiological and a pathophysiological function, which is why their elevation or action in the body may be indicative of diseases[28,30].

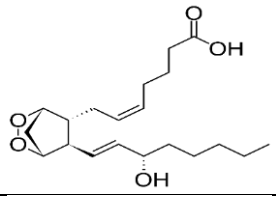
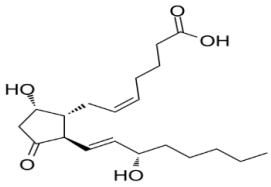
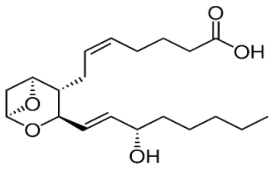
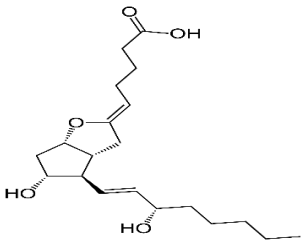
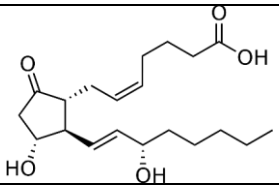
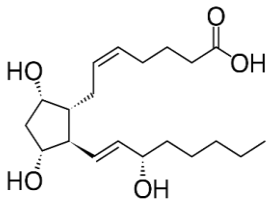
Function of the prostanoids

Each prostanoid has a specific function in the body. Such molecules can act together and manifest antagonistic effects; for example, thromboxane A_2 and prostacyclin I_2 have opposite functions[8]. TXA_2 is synthesized by the enzyme thromboxane synthase, which is responsible for thrombus formation and therefore acts as a platelet aggregator and vasoconstrictor [21,32]. The elevated presence of this prostanoid can indicate thrombotic events, including cardiovascular diseases [48]. PGI_2 is produced by endothelial cells via the enzyme prostacyclin synthase and acts as a vasodilator. Vasodilation has an inhibitory effect on thrombus formation since it ensures blood flow in the tissues [1,54].

The high concentration of TXA_2 promotes alterations in the arteries of rats, causing both increased contraction activity and an increase in thromboxane TP receptors in blood vessels, as well as hypertension [25].

Selective inhibition of TXA_2 contributes to alleviate oxidative stress and neuroinflammation [9]. In addition, research shows that this prostanoid functions as a biomarker, since high levels of the hormone or its TP receptor have been associated with the presence of tumors. Its overexpression manifests itself, in most cases, due to metastasis or can cause reduced survival of the patient [4]. Table 1 shows the role of prostanoids synthesized from AA.

Table no 1: Effects of prostanoids biosynthesized by the action of COX-2

Prostanoids	Molecular structure	Mechanism of action	Reference
PGH_2		Precursor of all prostanoids	[20]
PGD_2		Bronchoconstriction and increased airway response to histamine	[40]
TXA_2		Platelet aggregation and vasoconstriction	[44]
PGI_2		Inhibition of platelet aggregation and increased blood flow	[8]
PGE_2		Bronchodilator, tumor growth and proliferation, biomarker of cystic fibrosis severity	[11, 66]
$PGF_2\alpha$		Development of embryos and assists in luteolysis	[23]

PGE_2 is secreted mainly by endothelial cells and can be a precursor of $PGF_{2\alpha}$ through the enzyme 11 or 9-ketoreductase [8]. Such prostaglandins are similar in chemical structure, with the exception of the hydroxyl group at C9 of $PGF_{2\alpha}$ [10]. Both substances also contribute to the formation of edema, which is caused by increased blood flow to the affected region due to vasodilation [63].

According to research, the concentration of PGE_1, PGE_2 and $PGF_{2\alpha}$ was elevated in aqueous fluid of patients with macular edema secondary to retinal vein occlusion [63]. The same effect was observed in mice with induced intracerebral hemorrhage; however, after inhibition of the PGE_2 signaling pathway and its E_2 receptor, cerebral edema and neuroinflammation were reduced[22].

PGE_2 is also involved in tumor formation since elevated synthesis of the hormone contributes to the development, growth and invasion of cancer. Therefore, substances that inhibit the action of thi prostaglandin

possess antitumor activity [45]. The synthesis of PGE_2 can also be triggered by the cAMP (cyclic adenosine monophosphate) activation pathway and PKA (protein kinase A), which signals COX-2, promoting the migration and invasion of renal malignant tumors[57]. Exposure to the toxic metal cadmium induces this behavior in renal cancer because the concentration of PKA and COX-2 enzymes is high in these cells, making them dependent on the previously cited metabolic pathway[57].

In addition, in the nervous system, prostaglandin E_2 acts as a thermoregulator, and is able to increase body temperature (fever). Substances that inhibit the PGE_2 biosynthesis pathway have antipyretic activity and may contribute to the development of new drugs[18].

When synthesized by the COX-1 pathway, prostacyclin and prostaglandin E have a cytoprotective role in tissues, for example, in the gastric mucosa, they elevate mucus secretion and reduce hydrochloric acid levels[43]. For this reason, non-selective inhibitors, i.e., those that act by inhibiting both enzymes, have a tendency to present side effects related to gastric problems[24]. On the other hand, research has shown that the use of selective COX-2 inhibitors was associated with cardiovascular risk due to the biosynthesis of metabolites with platelet aggregating activity by COX-1 [2,46]. Given this situation, selective inhibitors have been studied in conjunction with cardiovascular safety profiles in order to associate them with cardioprotective substances to promote homeostasis and efficiency in treatment[3]. Other research has studied the inhibition of enzymes that catalyze the reaction in the final composition of the metabolic pathway, for example, the mPGES, in regards to the transformation $PGH_2 \rightarrow PGE_2$ [18].

$PGF_{2\alpha}$ interferes with the menstrual cycle through regression of the corpus luteum after ovulation[36]. In the uterus, this prostaglandin is produced in the endometrium and, when its concentration rises, the level of progesterone tends to reduce along with the corpus luteum, at which time the body understands that there is no pregnancy since progesterone is responsible for fixing the embryo in the uterus[53].

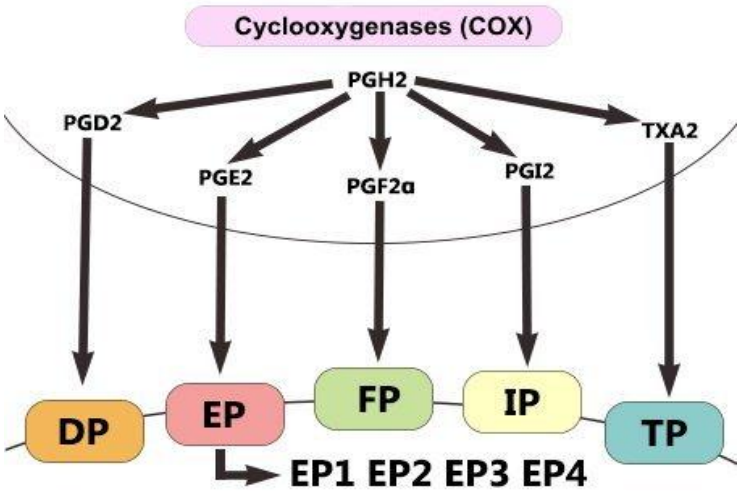
According to research, menstruation is an inflammatory process, in which there is an increase in prostaglandins, in essence, PGE_2 and $PGF_{2\alpha}$. The symptoms of menorrhea and dysmenorrhea in the menstrual period are associated with the elevation of these hormones [10].

The hormone PGD_2 is secreted mainly as a result of allergic disorders. The pro-inflammatory effect of this prostaglandin potentiates the response to histamine by the airways, where it also acts as a bronchoconstrictor [16]. On the other hand, prostaglandin E_2 deficiency tends to cause anaphylaxis, due to its vasodilating and relaxing action in the bronchi, in addition to promoting homeostasis in anaphylactic shocks [50,61].

Because it is associated with allergic episodes, the mechanism of action of PGD_2 is addressed in studies that mainly involve the treatment of asthma, along with PGE_2, which has an antagonistic effect [34,52]. In one study, the presence of eicosanoids in condensates exhaled by asthmatic patients was verified, and it was found that the levels of PGD_2 and the leukotriene receptor CysLT were elevated in relation to the healthy group[59]. In the same study, a correlation was found between the levels of this prostaglandin and the reduction of lung function.

For the effect of hormones to be manifested, it is necessary that cell membranes have their specific receptors and that cell signaling is possible [56,58]. Figure 4 highlights the mechanism of action of prostanoids and their cellular receptors, PE, FP, DP, IP and TP, as well as the subdivisions of such channels due to their specificity in receiving hormones, for example, from EP_1 to EP_4 for PGE_2 [1]. Also noteworthy is the intracellular signaling of prostanoids in cells neighboring those in which they were synthesized.

Figure no 4: Series 2 prostanoids and their specific receptors.



COX-1/2 participate in distinct physiological processes. While COX-1 has as its main function the cytoprotective role and homeostasis, COX-2 is activated only by response to inflammation, generating mainly series 2 prostanoids [38].

Non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and acetylsalicylic acid, act by inhibiting the metabolic pathway of cyclooxygenases [6,26]. However, steroidal anti-inflammatory drugs (SAIDs), which are corticosteroids, have an action that inhibits phospholipase enzymes, thus preventing the release of AA in the cytosol [19].

II. Conclusion

Arachidonic acid, dihomo-gamma-linolenic acid, eicosapentaenoic acid and docosahexaenoic acid are polyunsaturated fatty acids that are precursors of eicosanoids. The first lipid mentioned being responsible for the biosynthesis of the ones whose inflammatory potential is high. These inflammatory substances are series 2 prostaglandins. Advances in the discovery of new enzymes that participate in the biosynthesis of eicosanoids help us to understand the metabolic process. In addition, they contribute to the development of research involving pathophysiological processes and the potential of bioactive substances in biological activities.

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