

## Arachidonic Acid (AA, ARA) Derivatives

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In joint pain, it is mostly the cartilage that is inflamed and chronic headaches often result from neural inflammatory processes. 'Super hormones' exist, which can regulate the hormonal balance of the body. These super hormones are eicosanoids, derivatives of arachidonic acid, which is an omega-6 fatty acid. This article discusses the effect of arachidonic acid derivatives on the body and how inflammatory responses can be influenced and managed.



### Substance Class and Structure

Arachidonic acid (Latin, Arachis: 'peanut') belongs to the **family of lipids, more specifically, the fatty acids**. By definition, fatty acids consist of hydrocarbon chains of different lengths, with a carboxylic acid group (-COOH), which is present physiologically in its dissociated form (-COO<sup>-</sup>). Carboxylic acids with a chain length of 4 or more carbon atoms are referred to as fatty acids.

The hydrocarbon atoms of the chain are linked by single and double bonds. Each of the carbon atoms that are part of the double bond has only 3 binding partners and therefore, is not completely saturated with H atoms. These are called unsaturated fatty acids. Arachidonic acid consists of 20 carbon atoms and 4 double bonds (C<sub>20</sub>:<sub>4</sub>), which take on the spatial configuration of a trapezoid. These are cis double bonds.

In chemical nomenclature, the terms cis- $\Delta^{5,8,11,14}$ -arachidonic acid and eicosatetraenoic

acid are used as synonyms for arachidonic acid.

## Occurrence

In contrast to the fully saturated arachidonic acid (eicosanoic acid, C20:0), which can be isolated from peanuts, C20:4-arachidonic acid is not found in any plant. **Humans can acquire arachidonic acid through animal fats in food**, or synthesize it from the essential omega-6 fatty acid – linoleic acid – through the intermediates  $\gamma$ -linolenic acid and dihomo- $\gamma$ -linolenic acid. Thus, arachidonic acid is semi-essential.

Physiologically, arachidonic acid is inactive and is present in the esterified form, bound to membranes as phospholipids. **Eicosanoid biosynthesis begins in the event of:**

- Cell activation by mechanical trauma
- Ischemia
- Other physical perturbations
- Attack by pathogens
- Stimuli from nearby cells
- Tissues
- Pathogens such as chemotactic factors
- Cytokines, growth factors, and even certain eicosanoids

Activated cells then mobilize the enzyme CPLA2 (cytosolic phospholipase A2), capable of releasing  $\omega$ -6 and  $\omega$ -3 fatty acids from membrane storage. These fatty acids are bound in ester linkage to the SN2 position of membrane phospholipids and CPLA2 acts as an esterase to release the fatty acids.

Because of their lipophilic character, fatty acids pass through membranes and cannot be stored in vesicles. Their release is subject to a strict regulatory mechanism of the enzyme, which can only be activated by phosphorylation and the simultaneous binding of calcium. Extracellular signaling molecules, such as hormones and cytokines, may cause activation of the enzyme. Release only takes place when necessary!

## Eicosanoids – Derivatives of Arachidonic Acid

Prostaglandins, thromboxane, and leukotrienes are **summarized under the group name eicosanoids** (Greek, eikosi = 20). They are mediators (messengers) and mediate various effects in the human organism, similar to hormones. Their lifespan ranges from a few seconds to minutes, which strongly limits the scope of their mediation. However, unlike hormones, they are not transported to the periphery via the blood. They act either in a paracrine fashion on localized neighboring tissue or in an autocrine fashion on the producing cell itself.

Eicosanoids are neither synthesized in special glands (like glandular hormones) nor in specialized individual cells (such as growth hormones). All mediators mentioned above are derivatives of polyunsaturated C20 fatty acids, in particular, arachidonic acid C20:4, and are, therefore, referred to as arachidonic acid derivatives.

Other mediators are, for example, nitric oxide, a strong vasodilator, as well as histamine and bradykinin, which play a significant role in inflammatory reactions.

The 3 most important substance classes of eicosanoids are prostaglandins, thromboxane, and leukotrienes. These 3 substance classes are further subdivided into 2 groups which result from the respective enzyme involved.

Cyclooxygenase (COX) catalyzes the cyclooxygenase pathway that produces prostaglandins and thromboxane. Lipoxygenase catalyzes the lipoxygenase pathway that produces leukotrienes.

## Prostaglandins and Thromboxane

The name prostaglandin is derived from the prostate because the substance was isolated for the 1st time from this gland. Thromboxanes derive their name because of their relevance in thrombocytes.

### Biosynthesis

In order to produce prostaglandins and thromboxane, arachidonic acid has to initially enter the smooth endoplasmic reticulum where COX is found.

#### First, COX causes:

- Formation of endoperoxide
- Prostaglandin H<sub>2</sub> formation
- Cyclization and oxygenation of the ring

Because of this fundamental synthesis, COX is also referred to as PGH<sub>2</sub> synthase. Prostaglandin H<sub>2</sub> is the initial substance for all prostaglandins and thromboxanes. The derivatives of prostaglandin H<sub>2</sub> differ from each other only in the position of the keto group and the hydroxyl group in the original prostaglandin H<sub>2</sub>.

### Prostaglandins

As a derivative of PGH<sub>2</sub>, prostaglandins contain a cyclopentane ring.

Isomerases and reductases produce prostaglandins E<sub>2</sub> (PGE<sub>2</sub>) and F<sub>2</sub>α (PGF<sub>2</sub>α). Through the activity of prostacyclin synthase, prostaglandin I<sub>2</sub> (PGI<sub>2</sub>) is produced.

### Thromboxane

All thromboxanes have an oxane ring (cyclopentane ring and oxygen). Thromboxanes are synthesized in thrombocytes. From PGH<sub>2</sub>, thromboxane A<sub>2</sub> (TXA<sub>2</sub>) is 1st formed via thromboxane synthase, resulting in the synthesis of more thromboxanes.

### COX-I and COX-II

COX **exists in 2 isoforms that perform different tasks**. Clinically, this enzyme is very important because it is the target of acetylsalicylic acid (ASA, aspirin).

COX-I is produced continuously (constitutive) and is always active. Its presence in the gastrointestinal tract and kidneys is important since the inhibition of COX-I (for example, aspirin) can have serious side effects.

COX-II is not present ubiquitously, but only in some cells, particularly in leukocytes and macrophages of the immune system. Its activity can be induced by cytokines, growth factors, and endotoxins. COX-II is responsible for 3 effects which are the reason why COX inhibitors are commonly prescribed: They produce prostaglandins, which results in pain, fever, and inflammation.

# Effect of Prostaglandins and Thromboxanes at the Molecular Level

Prostaglandin and thromboxane are hydrophilic, which is why they cannot diffuse freely across membranes. Thus, they require binding to membrane receptors, which are intracellularly linked to a heterotrimeric G protein and trigger a specific ongoing reaction cascade. To date, **5 main types of receptor classes are known**. Depending on the type of receptor, inhibition or stimulation of adenylate cyclase with a corresponding decrease or increase in intracellular cAMP concentration occurs.

1. EP receptor binds PGE<sub>2</sub>. The subtype EP<sub>1</sub> acts via cAMP increase, the subtype EP<sub>2</sub> acts via the IP<sub>3</sub> mechanism.
2. FP receptor binds PGF<sub>2</sub> via the IP<sub>3</sub> mechanism.
3. IP receptor binds PGI<sub>2</sub> via cAMP increase.
4. DP receptor binds PGD<sub>2</sub> via cAMP increase.
5. TP receptor binds TXA<sub>2</sub> via the IP<sub>3</sub> mechanism.

Prostaglandin E <sub>2</sub>	'Main' prostaglandin	Formation via COX-I protects gastric mucosa by mucus production. Formation via COX-II acts on the inflammatory process, pain sensitization, and temperature increase.
Prostaglandin F <sub>2</sub> α		Stimulation of stomach mucus production (protective function), vasodilation, bronchoconstriction
Prostacyclin PGI <sub>2</sub>	Synthesis in endothelial cells	Inhibition of platelet aggregation, vasodilation
Thromboxane A <sub>2</sub>	Synthesis in thrombocytes, an opponent of prostacyclin	Promotes platelet aggregation, vasoconstriction

The demand release, production, and modulation of eicosanoids are triggered via stressing stimuli on 1 hand, and on the other hand, via other mediators such as histamine and bradykinin and gastrointestinal hormones such as gastrin.

The biological action of prostaglandins and other eicosanoids is extremely complex and at this point not fully understood. To recognize a single operating principle is difficult because numerous compounds act synergistically or antagonistically in some cases. Not only does the absolute amount of these mediators play an important role, but also the proportion of each mediator with respect to the others is contributory.

## Aspirin as an Inhibitor of COX

Aspirin is present in almost every medicine cabinet in households around the world. Whether it is pain in the head and neck area, menstrual problems or a toothache, fever or colds - aspirin is the 'superstar' among analgesics and therefore often the 1st drug of choice when it comes to alleviating the symptoms.

**The over-the-counter merchantability of this painkiller in pharmacies is currently debated by the public** with respect to the responsible management of this drug by patients. In long-term studies, research on patient compliance in everyday life has been conducted. Results showed that consumers maintained a responsible attitude and were adhering to the information in the package insert for dosage and method of administration.

Aspirin, synthesized by the Leverkusen company Bayer AG since the beginning of the 20th century, is 1 of the longest researched medicines. The world health organization placed the drug on its list of essential medicines in 1977.

The active ingredient acetylsalicylic acid is distinguished by its many properties: it acts as an inhibitor of platelet aggregation, as a pain reliever (analgesic), to lower fever (antipyretic), and as an anti-inflammatory drug.

Its mechanism of action is based on an irreversible inhibition of  $\text{PGH}_2$  synthase, more specifically, of COX-I and COX-II. This results in the decreased formation of inflammatory prostaglandins and corresponding mitigation of the symptoms caused by prostaglandins. Since prostaglandin is also involved in the production of the mucus that protects the gastric epithelium, the intake of aspirin in high doses or with prolonged ingestion leads to stomach discomfort, bleeding, heartburn, or vomiting.

In order to minimize these side effects, the pharmaceutical industry has developed COX inhibitors that specifically inhibit COX-II alone. These drugs are still in the testing phase.

## Body Reaction: Fever

Fever is the body's response to an infectious disease. The cytokines interleukin-1 and  $\text{TNF-}\alpha$ , which are distributed in the blood migrate to the hypothalamus, where they induce the release of  $\text{PGE}_2$ . This prostaglandin produces a set point adjustment at the temperature regulation center and fever occurs.

## Effect of Prostaglandin on Birth

$\text{PGE}_2$  and  $\text{PGF}_2\alpha$  have an effect on the uterus and trigger uterine contractions during birth. Pharmacologically, this effect can be modulated to imitate contractions for the early induction of labor, for instance, or to inhibit them in order to avoid premature birth.

## Breakdown of Prostaglandin and Thromboxane

The breakdown of prostaglandins occurs in 2 steps. In the 1st and quicker step, widely occurring specific enzymes lead to the inactivation of prostaglandins, which are then broken down in the 2nd (somewhat slower) step in oxidation reactions (e.g.,  $\beta$ -oxidation in the liver).

After a half-life of about 30 seconds, thromboxane  $\text{A}_2$  breaks down into the inactive but stable thromboxane  $\text{B}_2$ .

## Leukotrienes

Unlike prostaglandins and thromboxanes, **leukotrienes are formed only in a few types of cells** – mainly in macrophages, mast cells, and granulocytes. As already described, the polyunsaturated arachidonic acid serves as a starting compound.

Several isoenzymes of lipoxygenase (exist, of which only 5-lipoxygenase) can produce leukotrienes. In contrast to COX, lipoxygenase is located in the cytoplasm and is mainly found in leukocytes and macrophages.

Intracellular increase in calcium levels activates 5-lipoxygenase, resulting in a release of leukotrienes.

Through the incorporation of molecular oxygen, 5-lipoxygenase turns arachidonic acid into hydroperoxide. First, 5-hydroperoxy eicosatetraenoic acid (5-HPETEs) is formed, which serves as an unstable precursor of all leukotrienes. The double bonds are then transferred, and leukotriene A<sub>4</sub> (LT A<sub>4</sub>) is created, which in turn is the origin of the 2 most important main groups of leukotrienes: LTB<sub>4</sub> and peptide leukotrienes. LTB<sub>4</sub> is produced by hydrolysis, while peptide leukotrienes are produced by the addition of glutathione to LTA<sub>4</sub> through a thioether.

### Effect of leukotrienes at the molecular level

Like other arachidonic acid derivatives, **leukotrienes play an important role in the inflammatory process**. The precise molecular mechanism of action is largely unknown. It is known that leukotrienes are among the most potent constrictors of the bronchial muscles and therefore, play an important role in pathophysiologies involving these muscles.

Just like prostaglandins, leukotrienes act on membrane receptors that lead to the activation of phospholipase C.

BLT receptor	Binding of LTB <sub>4</sub>	Leukocyte membrane
CysLT receptor	Binding of peptide leukotrienes	Membrane of smooth muscle cells

Different leukotrienes can be distinguished: LTA<sub>4</sub>, LTB<sub>4</sub>, LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub>. While LTA<sub>4</sub> is only an intermediate product, the biologically active forms are especially LTB<sub>4</sub> and LTC<sub>4</sub>.

LTB<sub>4</sub> is secreted by macrophages in the event of inflammation in order to attract leukocytes (chemotaxis). LTB<sub>4</sub> increases vascular permeability, leading to fluid accumulation in the extracellular space and inflammation-associated swelling.

Peptide leukotrienes are involved in the development of bronchial asthma, due to their strong bronchoconstriction effect. In particular, LTC<sub>4</sub> and LTD<sub>4</sub> have approx. 1,000 times the potency of histamine.

Clinical note: The above-mentioned context clearly shows why antihistamines can only very weakly counteract bronchial asthma as bronchoconstriction is primarily caused by leukotrienes. The most important drugs are still synthetic glucocorticoids, which inhibit PLA<sub>2</sub> and thus - relatively, in a non-specific manner - the formation of arachidonic acid derivatives, including leukotrienes.

### Breakdown of leukotrienes

The breakdown of leukotrienes takes place in the liver. Oxidation reactions take place in the peroxisomes of hepatocytes and leukotrienes are converted into biologically inactive metabolites, which are excreted in the bile.

## The Role of Eicosanoids in Allergic Reactions

An allergy occurs when a normally harmless antigen triggers an overreaction of the body's immune system. This reaction is also called a hypersensitivity reaction (asthma is a Type 1 hypersensitivity). The sensitive organism responds differently than normal (Greek *allos* = different, Greek *ergon* = work).

Allergies in a narrower sense are caused by an IgE-mediated release of histamine with immediate symptoms (immediate hypersensitivity). Histamine is synthesized by the decarboxylation of the amino acid histidine and is stored in the granules of mast cells. A matching antigen contact causes the breakdown of histamine-storing granules

(degranulation) and the release of the mediator. Histamine is the most important mediator of immediate (or type 1) hypersensitivity reactions.

The effect of histamine is mediated via the specific H1 receptor. Typical symptoms are itching, increased mucus production, edema, vasodilation of the arterioles and venules, as well as bronchoconstriction, which is mainly involved in the pathogenesis of asthma.

Shortly after histamine release, PLA<sub>2</sub> is activated in the mast cells, leading to the above-described release of arachidonic acid from the lipids in the plasma membrane.

**Pharmacologically, each level of allergy development can be affected, resulting in the alleviation of the symptoms as follows:**

- Cromoglycate impedes the release of mediators from mast cells.
- Antihistamines (H1-blockers) prevent the binding of histamine to the receptor.
- Anti-leukotrienes act antagonistically to leukotrienes, but for some people, the 1st try can be disappointing.
- Cortisone reduces the activity of PLA<sub>2</sub> and inhibits the production of interleukins. The mechanism is not yet understood. Due to its very effective action, it is still the most important treatment for symptomatic asthma.

## References

Arachidonic Acid. (n.d.). *Encyclopedic Reference of Immunotoxicology*,49-49.  
doi:10.1007/3-540-27806-0\_114.

Dumancas, G. G., Murdianti, B. S., & Lucas, E. A. (2013). *Arachidonic acid: Dietary sources and general functions*. New York: Nova Science Publishers, Inc.

Mallion, K. B. (n.d.). Chemistry of the prostaglandins. *Aliphatic Chemistry*,240-289.  
doi:10.1039/9781847555540-00240.

Marnett, L. J. (1985). *Arachidonic acid metabolism and tumor initiation*. Boston: Nijhoff.

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