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Review

Arachidonic acid metabolism and its use in the diagnosis of mastocytosis

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Abstract: Mast cells and basophils degranulate upon activation, releasing preformed mediators from intracellular granules into the extracellular environment, of which tryptase and histamine are the two most common and best characterized mediators. Despite the large number of mediators synthesized by mast cells, the non-tryptase biomarkers used to evaluate systemic mastocytosis and mast cell activation syndrome do not include the metabolites of the prestored amine histamine and the *de novo* synthesized phospholipids prostaglandin D2 and leukotriene C4. Currently, these markers are not used as criteria for the diagnosis of mastocytosis and mast cell activation syndrome. However, consensus groups foster the use of increases in measured baseline levels of these metabolites as potential diagnostic criteria. Metabolites of arachidonic acid such as prostaglandin D2 or leukotriene C4 play a role in the development of symptoms in systemic mastocytosis and mast cell activation syndrome. In this review, the metabolites of arachidonic acid and the detection of the metabolites of leukotrienes and prostaglandins in mastocytosis are highlighted. Measurement of these metabolites remains a major challenge because they are not widely available in daily clinical practice. However, new insights have been gained in recent years, and their application in the clinic has progressed.

Keywords: systemic mastocytosis; mast cell activation syndrome; arachidonic acid; metabolites; prostaglandin D2; leukotriene C4

1. Introduction

Mast cells (MCs) are immune cells of myeloid lineage and are found throughout the connective tissue of the body. Under normal circumstances, they are not found in the human blood except in malignant hematopoietic conditions. In the connective tissue, MCs are localized around blood vessels and do not belong to the perivascular system [1]. They were first described by Paul Ehrlich a century ago. Their cytoplasm contains 50–200 large granules containing numerous preformed mediators such as biogenic amines, enzymes, growth factors, peptides, proteoglycans as well as *de novo* synthesized mediators such as chemokines, cytokines, nitric oxide, and phospholipid metabolites [2]. Abnormal proliferation and infiltration of MCs in various tissues in one or more organs is called mastocytosis [3]. The diseases may present as cutaneous or systemic mastocytosis (SM) [3]. MC activation syndrome (MCAS) is a condition in which MCs release inappropriate and excessive amounts of mediators leading to severe, episodic symptoms in at least 2 organ systems including cutaneous, gastrointestinal, respiratory and cardiovascular symptoms [4].

MCs and basophils degranulate upon activation, releasing preformed mediators from intracellular granules into the extracellular environment, of which tryptase and histamine are the two most abundant and best characterized mediators [5]. Elevated tryptase and histamine levels can be detected in blood samples taken shortly after the onset of symptoms [3]. Thus, increased concentrations of histamine, histamine metabolites, prostaglandin D metabolites, and leukotriene C metabolites can also be measured in urine, serum, or plasma after anaphylactic reactions [3]. It should be noted that eosinophils can produce both prostaglandin D2 and cysteinyl leukotrienes in addition to MCs [6].

In SM and MCAS, MCs can be considered as to be responsible for the highest proportion of histamine released and subsequently measured histamine metabolites.

To date, the metabolites of prostaglandin D2, histamine, and leukotriene C4 have not been included in the criteria for the diagnosis of SM or MCAS, although there are reports of the use of these measurements to guide the treatment of SM and MCAS, including reports from before the discovery of tryptase [7]. Prostaglandin D2 and its metabolites thus appear to be a central element in the development of SM symptoms, as documented in two symptomatic patients with SM before the discovery of tryptase in 1980 [7]. Both patients had MC activation symptoms and elevated histamine; however, treatment with antihistamines was ineffective at preventing or treating acute attacks. High concentrations of the prostaglandin D2 metabolite 9α,11β-dihydroxy-15-oxo-2,3,18,19-tetranorprost-5-ene-1,20-dioic acid (PGD-M) were detected in the urine samples of both patients [7]. At that time, the additional administration of aspirin to the antihistamine treatment resulted in an 80–85% reduction in the clearance of this prostaglandin D2 metabolite and cessation of flushing and hypotension in one patient [7].

In the past, consensus groups have considered the use of the measurement of elevated levels of these metabolites from baseline as a potential diagnostic criterion for MCAS [8,9]. A detailed description of the inflammatory and anti-inflammatory function of each AA metabolite is beyond the scope of this review. The focus of this review is on the recent findings on the use of arachidonic acid (AA) metabolites as a potential diagnostic tool in SM.

2. The arachidonic acid metabolism

Arachidonic acid (AA) is an omega-6 polyunsaturated fatty acid (PUFA). The chemical formula is C20H32O2, 20:4(ω-6), where 20:4 refers to the 20 carbon atom chain with four double bonds and (ω-6) is the first position of the first double bond of the last omega carbon atom (Figure 1) [10].

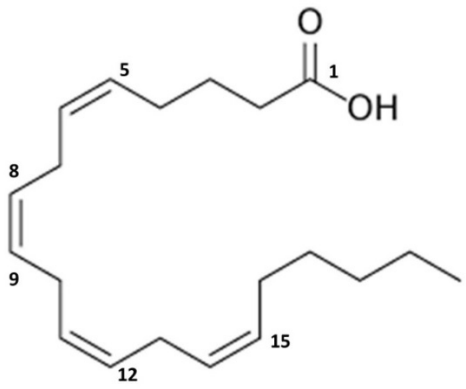

Figure 1. The molecular structure of arachidonic acid [10].

Arachidonic acid is naturally present in the structural phospholipids of the body's cell membranes or stored in the lipid bodies of immune cells [10]. It is particularly abundant in the phospholipids of skeletal muscle, brain, liver, spleen, and retina [9]. The concentration of free AA in blood is very low because albumin is very abundant in human plasma, which allows the binding of free fatty acids so that their concentration remains below 0.1 μmol [10].

The importance of AA lies in the fact that it can be metabolized by three different enzyme systems, such as cyclooxygenases (COXs), lipoxygenases (LOXs), and cytochrome P450 enzymes (Figure 2) [11].

2.1. The cyclooxygenase pathway

COXs are targets for non-steroidal anti-inflammatory drugs (NSAID) and COX-2-specific inhibitors called coxibs. COXs convert AA to prostaglandin H2, which is further converted by tissue-specific isomerases to prostaglandins (prostaglandin D2, prostaglandin E2, prostaglandin F2α), prostacyclin (prostaglandin I2), or thromboxane A2 (Figure 2) [10,11].

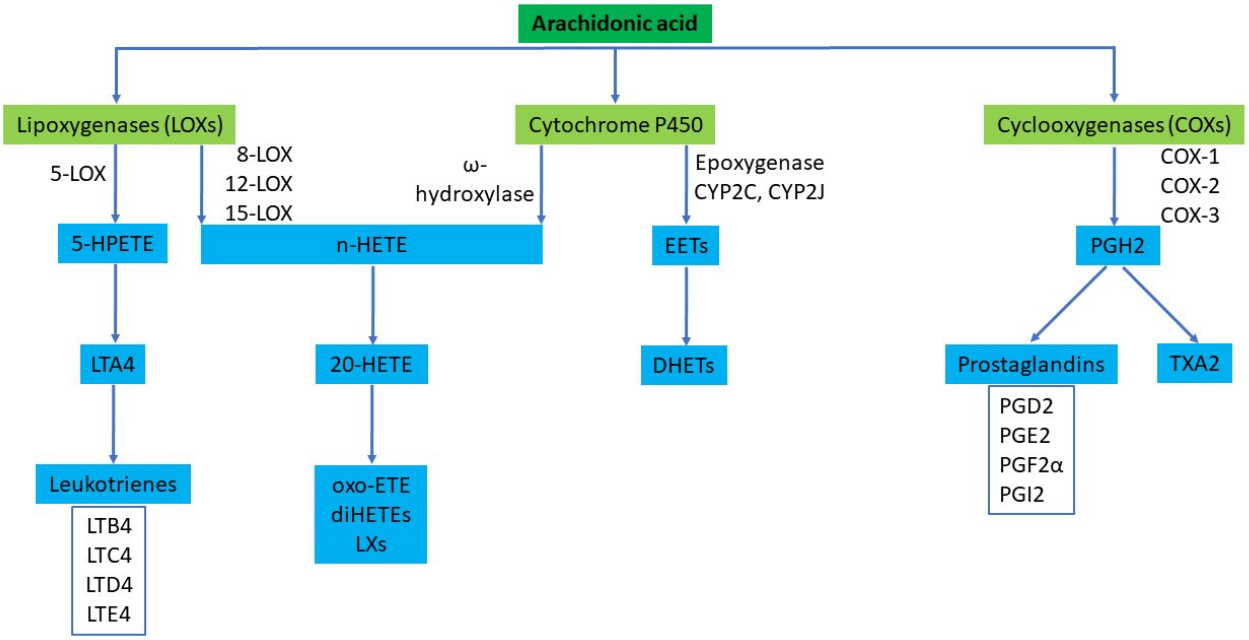

Figure 2. Schematic presentation of arachidonic acid metabolism. Adapted from reference [10]. AA: arachidonic acid; COX: cyclooxygenase; DHETs: dihydroxyeicosatrienoic acids; EETs: epoxyeicosatrienoic acids; HETE: hydroxyeicosatetraenoic acid; HPETE: hydroperoxyeicosatetraenoic acid; LOXs: lipoxygenases; LXs: lipoxins; PGH2: prostaglandin H2; PGD2: prostaglandin D2; PGE2: prostaglandin E2; PGF2α: prostaglandin F2alpha; PGI2: prostacyclin (prostaglandin I2); TXA2: thromboxane A2.

The first isoform is COX-1, also known as prostaglandin G/H synthase 1, prostaglandin endoperoxide synthase 1, or prostaglandin H2 synthase 1, an enzyme constitutively expressed in all tissues that induces acute inflammation in response to brief exposure to lipopolysaccharide and instructs the cell to promote or suppress leukotriene biosynthesis [10]. COX-1 is an enzyme that in humans is encoded by the PTGS1 gene [12,13] and is found in the perinuclear membrane or ER [10,11]. It couples with thromboxane synthase, prostaglandin F synthase, and two other prostaglandin D synthase isozymes to generate thromboxane A2, prostaglandin F2alpha, and prostaglandin D2, respectively.

The second, COX-2, also known as prostaglandin G/H synthase 2, or prostaglandin endoperoxide synthase 2, is an inducible isoform found in renal and brain macrophages and is upregulated by inflammatory stimuli such as bacterial endotoxin, cytokines, hormones, and growth factors after 3 to 24 hours of stimulation [10,11]. COX-2 is an enzyme encoded in humans by the PTGS2 gene [14], which preferentially couples with prostaglandin I synthase and three prostaglandin E synthases (cPGES, mPGES-1, and mPGES-2) to produce prostacyclin (prostaglandin I2) and prostaglandin E2 [10,11].

A new isoform, an enzymatically active splice variant of COX-1, COX-3, has been discovered in the brain and heart, but its function remains to be elucidated [10,11].

While COX-2 primarily metabolizes AA to prostaglandin G2, it also converts this fatty acid to small amounts of a racemic mixture of 15-hydroxyicosatetraenoic acids (e.g., 15-HETEs) [10,11,15]. The 15-HETE stereoisomers have intrinsic biological activities but, perhaps more importantly, can be further metabolized to lipoxins and epi-lipoxins [10,11,16,17].

2.2. Lipoxygenase pathway

Lipoxygenases (LOXs) are a family of iron-containing enzymes (non-heme) that act on free arachidonate. In this metabolic pathway, oxygenation can occur at many different AA positions, with an oxygen atom introduced at C-5, C-8, C-9, C-12, or C-15 by a series of lipoxygenase enzymes numbered according to the oxygen introduced at the carbon atom (e.g., 5-LOX, 8-LOX, 9-LOX) [9,10]. LOX products are derived from hydroperoxyeicosatetraenoic acid (HPETE). 5-HPETE and 15-HPETE are responsible for the production of leukotrienes and lipoxins [10,11,16,17]. Thus, the production of leukotrienes requires the enzyme 5-LOX to produce 5-HPETE, which is later converted to leukotriene A4 by the leukotriene synthase [10,11].

2.3. Cytochrome p450 pathway

Cytochrome p450 (CYP) enzymes contain a heme iron that is mainly expressed in the liver and other tissues and serves to eliminate toxins [10,11]. The CYP 450 pathway consists of two enzymes (cytochrome P450 epoxygenase and P450-ω-hydroxylase) [10,11], whose AA metabolism plays a yet unknown role in SM and MCAS.

3. Metabolism of prostaglandin D2 and the detection of its metabolites

Prostaglandin D2 is derived from AA by the sequential actions of COX-1 or COX-2 to generate prostaglandin H2, its precursor followed by the actions of hematopoietic (H-) or lipocalin (L-) prostaglandin D synthase [10,11]. The biological effects of prostaglandin D2 are mediated by activation of the D-prostanoid receptors DP1 and DP2 [10,11]. Basophils freshly isolated from bone marrow cells (primary basophils) are also capable of secreting prostaglandin D2 and prostaglandin E2. Although the amount of prostaglandin D2 released by primary basophils is less than that of MCs, the ability of primary basophils to generate prostaglandin E2 is stronger than that of MCs [18]. Prostaglandin D2 is subsequently converted to metabolites of the J-ring (15-deoxyΔ12,14-prostaglandin J2), the D-ring (tetranor-prostaglandin GM), and the F-ring (11β-prostaglandin F2α; 2,3-dinor-11β-prostaglandin F2α; PGD-M) by three pathways [19,20]. As early as 1985, F-ring metabolites in plasma (9α,11β-prostaglandin F2) and their 24-h urinary excretion were reported in a healthy subject and increased urinary excretion in a patient with SM [21].

In addition, increased urinary levels of the prostaglandin D2 D-ring metabolite have been reported in SM [22]. Reports have noted a marked increase in one or more prostaglandin D2 metabolites in urine samples within a 2 to 5 hour period after MCAS episodes, including anaphylaxis, induced asthma after aspirin exposure, or inhalation of mannitol [23–30]. Increased plasma levels of tetranor-prostaglandin GM as well as 11β-prostaglandin F2α have been documented in patients with

non-symptomatic SM, and plasma levels of tetranor-prostaglandin GM have been shown to increase more than 10000-fold in fatal MCAS [31].

4. Prostaglandin D2 metabolites in SM and in MCAS

Several studies have shown the utility of measurements of prostaglandin D2 metabolites in SM and in MCAS in both urine and plasma in comparison to tryptase or histamine.

Thus, baseline levels of 11β-prostaglandin F2α were elevated in 17 of 25 MCAS patients, and significantly more frequently than baseline levels of tryptase in 10 patients or urinary N-methylhistamine (N-MH) in 2 patients [32].

Urinary PGD-M concentrations in 46 samples from 17 biopsy-confirmed SM patients, were higher than N-MH concentrations. Even in four patients with normal excretion of N-MH, PGD-M excretion was elevated up to 300% above normal levels [33]. In addition, 57% of patients with MCAS had a single baseline or symptom-associated elevation of 11β-PGF2α, which was higher than the percentage of patients with elevated tryptase (29%), urinary leukotriene E4 (26%), or N-MH (3.9%) [34]. In patients with SM, a 24-hour urinary excretion of 11β-PGF2α > 3500 ng corresponded with a high degree to positive bone marrow biopsies. Furthermore, there was a significant positive correlation between 24-hour urinary excretion of 11β-PGF2α and serum tryptase levels [35]. In four patients with MCAS and SM-negative bone marrow biopsies, two patients had increased urinary prostaglandin F2α excretion; in the remaining two patients, baseline urinary 11β-prostaglandin F2α and N-MH levels were normal, with only urinary 11β-prostaglandin F2α excretion increasing significantly during acute MCAS. Interestingly, treatment with aspirin normalized the increased baseline urinary 11β-prostaglandin F2α excretion and prevented symptoms in all 4 patients [36].

5. Cysteinyl leukotrienes

Leukotriene C4 is the only cysteinyl leukotriene that is synthesized intracellularly via the 5-LOX and leukotriene C4 synthase pathways and then rapidly metabolized to leukotriene D4 and leukotriene E4 after transport by specific extracellular peptidases [37]. Leukotriene E4, a stable metabolite to monitor this pathway in plasma or urine. Although basophils also produce leukotriene C4, stimulated MCs produce over 20-fold more leukotriene D4 equivalents than comparatively stimulated basophils [38–40]. Each cysteinyl leukotriene has a preferred functional receptor that may contribute to the symptoms in SM and MCAS; type 1 cysteinyl leukotriene receptor ($CysLT_1R$) binds leukotriene D4, type 2 cysteinyl leukotriene receptor binds leukotriene C4, and type 3 cysteinyl leukotriene receptor binds leukotriene E4 [37].

6. Leukotriene E4 in SM

The urinary leukotriene E4 proved to be 48% sensitive and 84% specific for SM, and the combination of N-MH, 2,3-dinor-11β-PGF2α, and LTE4 measurements was 97% sensitive for SM with a specificity of 61% [41]. Increased urinary leukotriene E4 concentrations have been reported in MCAS and in some diseases in which eosinophils were the main source of cysteinyl leukotrienes [42,43].

There are numerous reports of increased urinary leukotriene excretion after insect bites, exercise, or drug-induced anaphylaxis [26,44]. Significantly increased urinary leukotriene E4 and 9α,11β-PGF2 levels were detected after allergen-induced anaphylaxis, but no increase in eosinophil-derived neurotoxin, suggesting that MCs, not eosinophils, are the source of leukotriene. Interval samples of urine showed that urinary leukotriene E4 levels were highest in a 3 to 6 hour collection interval after anaphylaxis, whereas 9α,11β-PGF2 levels were highest in the 0 to 3 hour interval. There was a significant correlation between the highest urinary leukotriene E4 levels and 9α,11β-PGF2 levels [25]. An increased urinary leukotriene levels in patients with SM has been described in several clinical reports in which cysteinyl leukotriene excretion correlated positively with concomitantly measured N-MH excretion [45] or with MC-related symptoms [46].

7. Conclusions

Tryptase and histamine are the two most abundant and best characterized granule mediators in MCs. As we have seen, the metabolites of AA may also play a crucial role in the diagnosis and onset of symptoms in SM. However, to date, the metabolites of prostaglandin D2, histamine, and leukotriene C4 have not been included in the criteria for diagnosis of SM. Therapeutic approaches were not discussed further in this review, as this is beyond the scope of this article. Undoubtedly, the use of NSAIDs and aspirin is an interesting approach to this disease in terms of AA metabolism. New evidence has emerged in recent years that supports the increased use AA metabolites measurements as diagnostic tool. Urinary measurement of prostaglandin D2 metabolites is promising and shows good sensitivity and specificity compared with tryptase and N-MH. However, the measurement of these metabolites remains a major challenge because the assays are not widely available in clinical practice. Because of the possible production of leukotrienes by eosinophils, the diagnostic use of leukotrienes should not be recommended in diseases with MACS-like symptoms. Great efforts are needed for well-designed randomized controlled trials that take into account multiple clinical and biological factors. Further, it cannot be excluded that other, as yet unknown, metabolites of AA play a role in SM. In the meantime, most laboratories rely on measuring serum tryptase to assess SM.

Conflict of interest

The author declares no conflicts of interest in this paper.

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