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Review article

Markers of anaphylaxis – a systematic review

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ABSTRACT

Anaphylaxis is defined as severe, life-threatening, systemic or general, immediate reaction of hypersensitivity, with repeatable symptoms caused by the dose of stimulus which is well tolerated by healthy persons. The proper diagnosis, immediate treatment and differential diagnosis are crucial for saving patient's life. However, anaphylaxis is relatively frequently misdiagnosed or confused with other clinical entities. Thus, there is a continuous need for identifying detectable markers improving the proper diagnosis of anaphylaxis. Here we presented currently known markers of anaphylaxis and discussed in more detail the most clinically valuable ones: tryptase, platelet activacting factor (PAF), PAF-acethylhydrolase, histamine and its metabolites.

Contents

1. Introduction

Anaphylaxis is defined as severe, life-threatening, systemic or general, immediate reaction of hypersensitivity, with repeatable symptoms caused by the dose of stimulus which is well tolerated by healthy persons [1]. Mast cells are the most important cells, involved in anaphylactic reactions. The mediators of these cells are: histamine, tryptase, serotonin, proteoglycans, proteases, chemotactic factors and *de novo* synthetized lipid mediators: prostaglandin D2 (PGD2), leukotriene B4 (LTB4), platelet activacting factor (PAF), cysteinyl leukotrienes (LTC4, LTD4, LTE4,), cytokines (TNF-alpha, IL-4, IL-5, IL-6, IL-8) [1–4]. Therefore, the proper diagnosis, immediate treatment and also differential diagnosis are crucial for saving patient's life. The measurements of potential markers of anaphylaxis could be helpful in this situation. In present, the measurements of tryptase levels are used in clinical practice [1–4]. Scientific reports revealed, that the activity of this enzyme, which is

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characteristic for mast cell granules, correlates well with the severity of anaphylactic reactions [1–4]. The measurements of levels of platelet activating factor (which causes the increase in vascular permeability) and PAF-acethylhydrolase, as well as histamine and its metabolites, could be also the valuable tool in cases of anaphylaxis.

Here we presented currently known markers of anaphylaxis and discussed in more detail the most clinically valuable ones: tryptase, platelet activacting factor (PAF), PAF-acethylhydrolase, histamine and its metabolites.

2. Material and methods

A search was started on 01.04.2015. using the MEDLINE/PubMed database (United States National Library of Medicine National Institutes of Health). The key words, used in the process of searching data; were as follows: anaphylaxis; mast cells; histamine; histamine receptors; tryptase; PAF. In order to select the data available in the literature, we performed the searching of the data using the following strategy: anaphylaxis – 19786; anaphylaxis AND clinical trial – 693; anaphylaxis AND review – 3012; anaphylaxis AND case report – 4764; anaphylaxis AND guidelines – 576; mast cell – 35164; mast cell AND anaphylaxis – 2418; histamine – 67318; histamine AND review – 8456; histamine AND anaphylaxis – 3474; histamine AND clinical trial – 6330; histamine AND anaphylaxis AND clinical trial – 96; histamine AND anaphylaxis AND case report – 351; histamine receptor – 21173; histamine receptor AND anaphylaxis – 535; tryptase – 3990; tryptase AND review – 569; tryptase AND anaphylaxis – 518; tryptase AND mast cell – 3342; tryptase AND clinical trial – 198; tryptase AND case report – 366; PAF – 10460; PAF and review – 830; PAF AND anaphylaxis – 280; PAF AND clinical trial – 297; PAF AND clinical trial AND anaphylaxis – 0; PAF AND case report AND anaphylaxis – 0. Filters: published since 1972 (in 1972 PAF was discovered). In January 2017, when we started the manuscript preparation, full-text articles were assessed for eligibility. In order to select the data available in the literature, we performed the searching of the data using the following strategy: anaphylaxis – 990; anaphylaxis AND clinical trial – 405; anaphylaxis AND review – 2263; anaphylaxis AND case report – 2304; anaphylaxis AND guidelines – 551; mast cell – 19803; mast cell AND anaphylaxis – 1347; histamine – 21096; histamine AND review – 3610; histamine AND anaphylaxis – 990; histamine AND clinical trial – 2157; histamine AND anaphylaxis AND clinical trial – 30; histamine AND anaphylaxis AND case report – 157; histamine receptor – 8551; histamine receptor AND anaphylaxis – 202; tryptase – 3132; tryptase AND review – 460; tryptase AND anaphylaxis – 464; tryptase AND mast cell – 2570; tryptase AND clinical trial – 128; tryptase AND case report – 287; PAF – 4046; PAF and review – 347; PAF AND anaphylaxis – 68; PAF AND clinical trial – 297; PAF AND clinical trial AND anaphylaxis – 0; PAF AND case report AND anaphylaxis – 0. Filters: published in last 17 years; full text.

From those full-text articles, 285 were selected for further analysis. In the final version of the manuscript, 168 articles were cited (5 clinical papers, 37 papers on mast cells and their functions in anaphylaxis, and papers on tryptase, histamine and PAF (n = 31, n = 34, n = 61, respectively)).

The search was mainly limited to studies written in English. 166 from 168 citations were found in MEDLINE. In the part of the manuscript, concerning clinical signs and symptoms, two Polish authors of chapters in textbooks were cited (Refs. [2,55]). Three citations, concerning tryptase in diagnostics of allergic diseases, anaphylactic reactions to low-molecular weight chemicals, and idiopathic anaphylaxis, were written in Polish in original versions (Refs. [14,17,163], respectively).

The process of searching for data is presented graphically according to PRISMA 2009 flow diagram in Fig. 1.

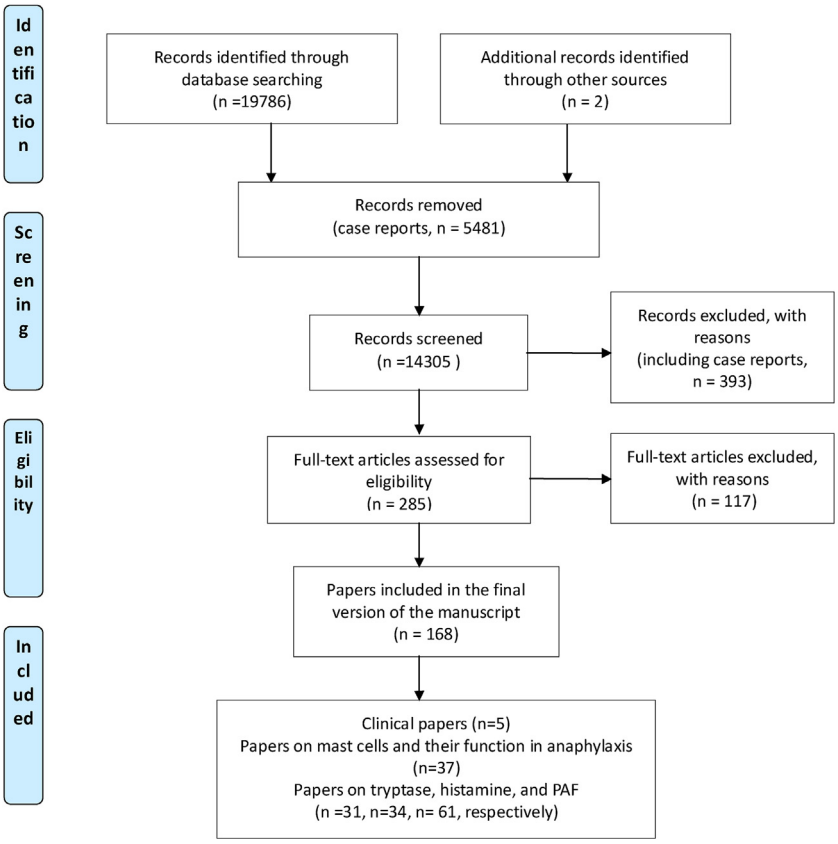

Fig. 1. PRISMA 2009 flow diagram [5].

3. Results and Discussion

3.1. Anaphylaxis – definition, clinical manifestations, differential diagnosis

The European Academy of Allergy and Clinical Immunology (EAACI) describes anaphylaxis as a severe, life-threatening, systemic or generalized, immediate hypersensitivity reaction. It is, in other words, a manifestation of objective, repeatable symptoms caused by an exposure to a stimulus of a strength that would be well tolerated by healthy individuals [1].

Anaphylaxis is not usually treated as a specific disease, but as a set of symptoms characterizing a specific reaction of people who are hypersensitive to various factors [2]. In the International Statistical Classification of Diseases and Related Health Problems ICD-10, it most closely matches an anaphylactic shock (T78.2). Clinical manifestations of anaphylaxis depend on the organs or systems affected. The clinical symptoms of hypersensitivity reactions, defined as anaphylaxis, can have a mild course and be of a local nature (hives, swelling) or give severe reactions with symptoms of shock (ie. a significant decrease in blood pressure, symptoms of airway obstruction) [2].

If one of the following criteria is fulfilled, the characteristic symptoms are very likely to be described as anaphylaxis [3]:

1 Respiratory reactions (shortness of breath, wheezing, stridor, hypoxemia);
2 Decrease in blood pressure and related symptoms from the other systems (syncope, fainting, coma, urinary incontinence);

Two or more of the following symptoms which occur suddenly after exposure to a probable triggering factor:

- symptoms of an acute nature, when the causative agent is unknown (duration from a few minutes to several hours) on the skin, mucous membranes (generalized itching, redness of the skin, swelling of the lips, tongue, uvula);
- respiratory symptoms (shortness of breath, wheezing, stridor, hypoxemia);
- decrease in blood pressure and related symptoms from other systems (syncope, fainting, coma, urinary incontinence);
- persistent symptoms from the gastrointestinal tract (abdominal pain, nausea, vomiting).

3 Decrease in blood pressure that occurs after exposure to a specific, known factor:

- infants and children: low systolic blood pressure (appropriate for the age group <70 mmHg for ages 1 month – 1 year; <70 mmHg + (age x 2) for group 1 year–10 years, <90 mm Hg for 11–17 years) or a decrease of systolic blood pressure over 30% of the initial value in relation to the value usually observed for that patient;
- adults: lower systolic blood pressure <90 mmHg or a decrease in systolic blood pressure over 30% of the initial value in relation to the value usually observed for that patient. The frequency of specific signs of anaphylaxis is shown in Table 1.

Symptoms suggesting anaphylaxis must be differentiated from other diseases of individual organs and systems [2]:

- skin and mucous membranes: chronic, transient physical urticaria; oral allergy syndrome,
- respiratory system: acute laryngitis and tracheitis; airway obstruction (foreign body, failure of the vocal cords),
- asthma attack (asymptomatic from other systems and organs),
- cardiovascular system: vasovagal syncope; pulmonary embolism, myocardial infarction, arrhythmias, hypertensive crisis,
- distribution shock associated with increased capacity of the vessels – due to enlargement of total volume of the vessels, without loosing the total blood volume (septic or neurogenic shock),
- reactions to toxicities or drugs: ethanol, food poisoning resulting from excessive histamine release after contact with food (scombroid food poisoning); opiates,
- nervous system: hyperventilation, anxiety disorders, somatization of psychological symptoms (vocal cord dysfunction, shortness of breath); dissociative disorders, epilepsy, psychosis, Hoigne type reactions, coma of various origins (metabolic, traumatic),
- endocrine system: hypoglycemia, thyroid breakthrough, carcinoid syndrome, pheochromocytoma, neuroendocrine tumors.

Table 1
Frequency of occurrence of clinical features of anaphylaxis [3,4, modified].

Skin/mucosa	Urticarial eruption
80–90%	Angioedema
	-oropharyngeal
	-laryngeal
	-intestinal
	Flushing
	Pruritus (palms/soles/oral/genitalia)
Bronchopulmonary	Laryngeal edema
60–70%	Wheeze/Cough
	Rhinitis
Cardiac	Hypotension/shock
40–50%	Reduced cardiac output
	Myocardial ischemia
	Hypotension/shock
	Reduced cardiac output
	Myocardial ischemia
	Arrhytmia
	Cardiac arrest
	Substernal pain
	Kounis syndrome
Gastrointestinal	Nausea
40–50%	Vomiting
	Diarrhea
	Intestinal edema
Neurological	Dizziness
<15%	Confusion
	Headache
	Feeling of impending doom
	Tunnel vision
	Syncope
	Seizures
Genitourinary	Uterine cramps (females)
<10%	Uterine bleeding (females)
	Scrotal edema (males)
Miscellaneous	Urinary/Fecal incontinence
<10%	

3.1.1. Role of mast cells in anaphylaxis

Mast cells are the primary cells that orchestrate majority of immediate allergic reactions [6]. Immature mast cells are produced in bone marrow and enter the circulation as mononuclear cell precursors [7]. The mast cell precursors express KIT receptors (proto-oncogene receptor tyrosine kinase) for stem cell factor on their surface [7]. Stem cell factor is a major cytokine which is crucial for mast cell growth, differentiation, development, proliferation, survival, adhesion, and homing [7]. From the circulation, mast cells migrate to all human tissues, even to the brain tissue which is unlikely to suffer from allergic reactions [7]. Once they enter the tissues, they differentiate and mature for several days, even weeks [7].

Another type of cells, involved in allergic reactions, are basophils. In contrast to mast cells, basophils mature in bone marrow from granulocyte precursors and enter the circulation as mature cells and they do not go into the tissues, going there only during the late stage of an allergic reaction [7].

Mast cells are present, in high number, in lungs, intestine, skin, nasal mucosa and conjunctiva [6]. Their location corresponds to the location of the most common allergy symptoms [6]. There are two types of mast cells: the first type are those whose granules contain only tryptase – mucosal mast cells (MC_T) (found mainly in pulmonary alveoli and intestinal mucosa), 2nd type are connective tissue-type mast cells (MC_{TC}), which contain – apart from tryptase – chymase, carboxypeptidase and cathepsin (located primarily in the skin, intestinal submucosa and blood vessels) [6,8,9]. Both cell types contain heparin and synthesize interleukins and other cytokines. MC_{TC} produce large amounts of interleukin-4 (IL-4) and IL-13 [6]. MC_T produce low amounts of IL-4 and IL-13 and large amounts of IL-5 and IL-6 [8].

Both subtypes of mast cells also vary in response to endogenous and exogenous stimulus causing their degranulation [8]. Both the MC_T mast cells, and MC_{TC} can be activated by immunoglobulin E, but only MC_{TC} cells can undergo activation by components of the complement (C5a) and substance P [8]. By contrast, only MC_T mast cell degranulate under the influence of PAF. Opioid receptors are expressed only on the MC_{TC} cells [8].

Both mast cell phenotypes differ in response to inhibitors of their degranulation [8]. Drugs known as mast cell stabilizers, such as cromolyn sodium and nedocromil, prevent only the degranulation of MC_T mast cells, by influencing the receptor associated with protein G (G-protein-coupled receptor 35) [8]. Both drugs do not currently play an important role in the treatment of anaphylaxis due to the lack of parenteral administration, and poor efficacy [8]. Sodium cromoglycate has been used in the treatment of some forms of mastocyte activation syndrome [8].

It is also worth mentioning that ketotifen, antihistamine of 1 st generation, in addition to its effect on histamine receptors, also affects the stabilization of the cell membrane of mast cells and can be used to prevent anaphylaxis in patients with idiopathic mastocyte activation syndrome [8].

Mast cells, and in particular tryptase released by them, play a central role in type I hypersensitivity reactions, according to Gell and Coombs [6].

Mediators of mast cells include: histamine, tryptase, serotonin, proteoglycans, proteases (chymase, carboxypeptidase), chemokines and synthesized *de novo* lipid mediators: prostaglandin D2 – (PGD2), leukotriene B4 (LTB4), platelet activating factor (PAF), cysteinyl leukotrienes (LTC4, LTD4, LTE4), cytokines (tumor necrosis factor alpha – TNF-alpha, IL-4, –5, –6, –8) [6].

The level of chymase, a serine protease enzyme, increases during anaphylaxis and correlates with the level of tryptase, and maintains in serum up to 24 h after the start of an anaphylactic reaction [10].

The level of carboxypeptidase also increases during an anaphylactic reaction (up to 8 h after the onset of symptoms), but no correlation with the levels of tryptase was observed. It was, however, elevated in patients with anaphylaxis, for whom tryptase levels were within normal range [10].

The study performed by Nassiri et al. has shown that during the activation of mast cells, an increased synthesis of products of arachidonic acid cascade, i.e. prostaglandin D2, and leukotriene C4 was observed in patients with anaphylaxis, which are then rapidly metabolized to 9α11βPGF2 and LTE4, respectively [11]. These metabolites exhibited a relatively high stability in body fluids (serum, urine) for about two hours after an anaphylactic reaction [11]. The authors have shown elevated levels of these metabolites in the serum of patients with anaphylaxis, compared to healthy subjects, and levels 9α11βPGF2 and LTE4 positively correlated with the severity of anaphylactic reactions [11].

During anaphylactic reactions, heparin is released, and complement system and factor XII are activated, leading to kininogen proteolysis and the release of bradykinin [8]. The degree of the complement system's activation and the level of bradykinin, correlate with the severity of anaphylactic reactions [12,13].

Brown et al. observed a positive correlation between the severity of anaphylactic reactions, and levels of tryptase, histamine, cytokines (IL-2, –6, –10), anaphylatoxin (C3a, C4a, C5a) and tumor necrosis factor receptor type I (TNFRI) [13]. In biphasic anaphylactic reactions, elevated levels of tryptase, histamine, IL-6, –10 and TNFRI were detected [13].

Mast cell degranulation can be induced by a variety of pathophysiological mechanisms, such as IgE-mediated reactions, alterations in arachidonic acid metabolism, complement system activation, direct effector cells degranulation, as well as by other unknown factors [6,14].

IgG antibodies, complement system components and substances that cause direct degranulation of mast cells, may play a role in the pathogenesis of anaphylactic reactions independent of IgE [15]. In IgG-dependent anaphylaxis, IgG/antigen complexes are formed. They bind with FcγRs receptors on mast cells, basophils and neutrophils, which results in release of mediators (PAF among others) from the granules of these cells [15]. IgG1, IgG3 and IgG4 antibodies are most likely involved in this type of reactions [15]. Clinical observations suggest that IgG-dependent anaphylaxis is induced by a parenteral administration of large amounts of antigen, for example a biological medical products (chimeric, humanized and human monoclonal antibodies), dextran, aprotinin or von Willebrand factor [15].

In the complement system-dependent anaphylactic reactions, binding of one or both of the components (anaphylatoxin – C3a and C5a) to their receptors on mast cells, basophils and other myeloid and endothelial cells, occurs [15]. It has been shown that anaphylatoxin levels in serum correlate with the severity of anaphylactic reactions, but this correlation is not as strong as in the case of tryptase or histamine [15]. Activation of the complement system is probably related to the intensification of anaphylaxis symptoms, caused by the wasp venom toxicity [15].

Anaphylaxis reactions, induced by substances directly activating the complement system, without IgG or IgE antibodies' participation, were also observed (dialysis membranes, protamine sulfate, application of intravenous drugs in liposome form, polyethylene glycol infusion) [15]. However, these observations had some limitations: firstly – complement's activation did not have to be the sole factor responsible for the anaphylactic reactions, secondly – inhibitors of complement's system activation were not used for humans, nor were anaphylatoxin receptor blockers, for the prevention of this type of reactions [15].

Anaphylactic reactions caused by certain drugs, such as oversulfated heparin, antibiotics (fluoroquinolones, vancomycin), opioids, anaesthetics (neuromuscular blocking agents among others), occur in the mechanism of direct degranulation of mast cells without the involvement of immunoglobulin or complement system [15]. Sulfonylated heparin directly activates the kininogen system and increases the production of bradykinin [15]. Non-steroidal anti-inflammatory drugs, including acetylsalicylic acid, block cyclooxygenase, by inhibiting the production of prostaglandins [15]. This causes a reduction in prostaglandin E2 level (PGE2), which is capable of alleviating anaphylactic reactions, and an increased synthesis of cysteinyl leukotrienes, which in turn induces bronchoconstriction and increased vascular permeability [15]. Vancomycin directly activates mast cells in an unspecified

mechanism, dependent on calcium and phospholipases C and A2 [15]. Opioids induce the release of histamine by, among others, binding with endogenous opioid receptors [15]. Fluoroquinolones and neuromuscular blocking agents, such as tubocurarine, directly activate mast cells by joining with MRGPRX2 receptor, coupled with G protein [15]. It is believed that drugs causing anaphylactic reactions may not only directly act on mast cells, but also through other, so far unknown mechanisms [15].

Participation of contact factor (factor XII) in the pathogenesis of anaphylaxis in humans and animals has also been described [16]. It has been proven that deficiency in or the use of factor XII inhibitors, plasma kallikrein, kininogen of a high molecular weight or bradykinin B2 receptor, inhibited allergen or IgE induced activation of mast cells in mice [16]. Activated mast cells release heparin, which provides a negatively charged surface for auto-activation of factor XII [16]. Activated factor XII initiates the production of plasma kallikrein, which in turn, by kininogen proteolysis, increases the release of bradykinin [16]. Sala-Cunill et al. showed that among patients in acute phase of anaphylaxis, an enhanced activation of factor XII, kallikrein and kininogen in plasma (compared with the initial concentrations of the above parameters or healthy individuals) occurs [16]. Furthermore, the authors found that during anaphylaxis, the level of heparin in plasma increases, there is an activation of the contact factor and increased production of bradykinin [16]. The contact factor system not only takes part in anaphylaxis pathogenesis, but also in the hereditary angioedema, and many diseases of inflammatory or allergic origin, such as bacteriemia, sepsis, vasculitis, rhinitis and asthma, and therefore, it appears to be a relevant factor in the development of new therapeutic strategies [16].

Some substances which induce mast cell degranulation are shown in Table 2.

Due to the increasing use of determining markers of anaphylaxis levels in clinical practice (tryptase) and potential targets for development for therapeutic strategies (histamine, PAF), the authors decided to discuss them in more detail in this paper.

3.2. Tryptase

This enzyme, which is a marker of anaphylactic reactions, characteristic for the granules of mast cells, is present in complexes with heparin with molecular weight of about 140 kD [18,19,20]. The gene responsible for the synthesis and metabolism of tryptase is located on the short arm of chromosome 16 [19,20]. 2 gene loci for tryptase are known (TPSAB1 and TPSB2) [21]. Trivedi et al. showed that there is a defense mechanism against the loss of gene function for tryptase in humans [21].

Tryptase is resistant to protease inhibitors, due to the unavailability of active enzyme's center facing inward [19,20]. There are four types of human tryptase (alpha, beta, gamma, delta) and corresponding subtypes [19,20].

Characteristics of different tryptase subtypes are shown in Table 3.

Alpha-tryptase is released continuously, and its concentration increases with the increase in the number of mast cells, whereas β-tryptase is excreted during a violent mast cell degranulation. Therefore, high concentration of alpha-tryptase is observed in patients with systemic mastocytosis, and the concentration of beta-tryptase is increased during anaphylactic reactions [19,20,22].

The multidirectional activity of tryptase was also described; it generates the formation of complement components C3a and C5a, sensitizes smooth muscles to histamine activity, induces chemotaxis of eosinophils, stimulates fibroblasts and fibrosis, inactivates fibrinogen, inactivates vasoactive intestinal peptide (VIP) [22].

Tryptase may be involved in progression and destabilization of atherosclerotic plaque in the ACS (acute coronary syndrome) [23]. The role of tryptase as a prognostic marker of cardiovascular complexity in ACS was recently evaluated by Pastorello et al. [24]. The association among tryptase levels and the angiographic extension of cardiovascular disease, as defined by the SX-score (cardiac surgery score) was reported [24].

In another study, performed on the ACS population (two groups: patients with MACE (major adverse cardiovascular events)

Table 2
Main mechanisms involved in human anaphylaxis [2,4,17, modified].

Mechanism	Trigger factor
IgE-dependent mechanisms	**IgE-mediated reactions**
	Hymenoptera venom
	inhaled allergens
	food allergens
	human proteins (e.g. insulin, vasopressin)
	medication allergy
	FDEIA (food dependent exercise-induced anaphylaxis)
	seminal fluid
	IgE-dependent reactions with haptens
	antibiotics
	anaesthetics (e.g. succinylcholine, pethidine)
	heterological sera
	disinfectants (formalin)
	low-molecular weight compounds (1,4-phenylenodiamine, 1,4-toluenodiamine, persulfates, metal salts)
IgE –independent mechanisms	**Alterations in arachidonic acid metabolism**
	acetylsalicylic acid and other NSAIDs
	Activation of complement system and anaphylatoxins production (C3a, C5a)
	gamma-globulins
	blood transfusions
	immunological complexes IgG/IgA
Direct degranulation of effector cells	hypertonic solutions (mannitol, radiocontrast media)
	drugs (opioids; antibiotics: vancomycin, polymixin; doxorubicin; dextran; hydralazine)
Unknown mechanisms	increased mast cell sensitivity/degranulation
	Th2-cytokine polarization
	glicocorticosteroids
	preservatives
	physical factors (exercise, cold, heat, sunlight)

Table 3
Tryptase subtypes characteristics [19,20,modified].

Type	Subtypes	Characteristics
Alpha-tryptase	Alpha I	- low biological activity
	Alpha II	- present in serum in small concentrations
Beta-tryptase	Beta I	- the main form of tryptase in mast cells granules
	Beta II	- relesased during inflammatory state; in healthy people not detected in serum
	Beta III	
Gamma-tryptase	Gamma I	- expressed in cell membrane of mast cells; its role is unknown
	Gamma II	
Delta-tryptase	Delta I	- its characteristic feature is shorter chain and different affinity to proteins
	Delta II	

and patients without MACE), Pastorello et al. revealed, that serum tryptase levels at admission and at discharge and SX-score were higher in patients with MACE than in those without [25]. The authors concluded, that serum tryptase level may be a non-invasive, promising prognostic long-term biomarker in ACS, STEMI (ST-elevation myocardial infarction) and NSTEMI (non-ST elevation myocardial infarction) patients [25]. Serum tryptase levels higher than 4.85 ng/mL at the onset of ACS were predictive for occurrence of MACE within 2 years from the acute event [25]. By contrast, no significant association between MACE and C-reactive protein (CRP), or maximum level of high-sensitivity troponin (hs-Tn) values was found [25]. Thus, tryptase could be a valuable, predictive marker of recurrent adverse events in ACS patients [25]. The correlation between high tryptase levels and the development of MACE indicates the role of mast cells in the process of coronary atherosclerotic damage, in which these cells contribute to plaque progression and destabilization [25].

Bot et al. explained the potential roles of activated mast cells in the growth and destabilization of an atherosclerotic plaque [26].

It is recognized, that mast cells are not only involved in allergic diseases but also in inflammatory conditions such as atherosclerosis [27] and thrombosis [28]. Atherosclerosis is an inflammatory disease characterized by the progressive accumulation of cholesterol in the intimal layer of arterial walls leading to the formation of plaque and vascular obstruction [29]. Mast cells are located in the human arterial intima and adventitia [30], and, upon activation, they release granules locally, containing a large panel of mediators, including neutral proteases (tryptase and chymase), cathepsins, heparin, histamine, cytokines, and growth factors [30]. During early atherogenesis, the effector molecules stimulate leukocyte recruitment and lipid accumulation in the evolving plaque, whereas during advanced stages of atherogenesis, they contribute to the generation of an unstable plaque susceptible to rupture [26]. Tryptase activates metalloproteinases (MMP), such as MMP-1, MMP-2 and MMP-3 and procollagenase and can promote plaque disruption or rupture [7,31,32]. It also promotes the degradation of lipoproteins (including HDL), fibronectin and vitronectin [7,31,32], acting as powerful inflammatory stimulus, leading to the endothelial dysfunction [33,34]. Tryptase also can degrade neuropeptides, such as calcitonin gene related peptide (CGRP) [7,32]. This protease can also activate neighboring cells by cleaving and activating protease-activated receptors (PAR) 2, including these located in platelets, and thrombin receptors [7,32], and catalyze fibrinogenolysis, thus leading to coagulation abnormalities (e.g. Kounis syndrome) [35].

Via its action on macrophage PAR-2 receptors, tryptase may be involved in macrophagic foam cell formation, thus promoting lipid accumulation at the initiation of atherosclerosis [36]. This effect can facilitate plaque formation and progression and, as a consequence, may lead to the development of cardiac diseases [36]. Moreover, the activation of matrix-degrading metalloproteinases promoted by tryptase could be a factor leading to plaque destabilization, which can consequence in major cardiovascular effects due to its rupture or erosion [32]. Persistent tryptase elevation has been detected in patients with coronary artery disease [37]. Given this context and the ability of tryptase to promote the coagulation cascade and the thrombotic process, tryptase appears to be one of the most important inflammatory mediators both in atherosclerosis and coronary pathology.

In healthy people, the basic level of tryptase in serum does not exceed 11.4 ng/mL [38]. The optimal time for determining tryptase levels is 1–6 h after exposure to the allergen (peak between 15 min and 2 h, half-life in serum 1.5-2.5 h). It is accepted that blood sample has to be collected the within 1–2 h following the onset of anaphylactic reaction [39]. However, enhanced tryptase levels can decrease within next 12–14 h [39]. Elevated levels of tryptase, in addition to anaphylactic reactions, are observed in other diseases and conditions such as wound healing, scar formation, multi-organ injuries, hypoxia, myocardial infarction, heroin poisoning, mastocytosis, acute myelogenous leukemia, myelodysplastic syndromes [22]. In patients with mastocytosis, confirmed by bone marrow biopsy, tryptase concentration was > 20 ng/mL (in healthy humans of <14 ng/mL) [40]. Tryptase level above 20 ng/mL is one of the diagnostic criteria for the disease, however, it is not the specific marker [41].

Elevated tryptase concentration may persist for up to 3 days from death due to anaphylaxis [42], especially in the case of parenteral exposure to the allergen (insect stings, parenteral drugs' administration) [43]. There was a correlation between tryptase concentration and severity of anaphylaxis in patients sensitive to Hymenoptera venom. In patients with mild reactions, tryptase levels were normal, while in 30% of patients whose levels of tryptase exceeded 13.5 ng/mL, systemic reactions occurred [44]. In people allergic to Hymenoptera venom, basic tryptase concentration correlated with the severity of anaphylaxis after a sting [45]. It was also shown that patients allergic to insect venom with elevated basic tryptase concentration are more at risk of anaphylaxis during immunotherapy [46].

Post-mortem measurement of tryptase levels can be useful if anaphylaxis is suspected to be the cause of death, especially in cases of sudden death due to unknown causes [47]. Serum for this marking should be collected up to 15 h from the time of death [47]. Elevated levels of tryptase were observed in 12% of adults who died suddenly, and more than 40% of infants – victims of sudden infant death syndrome [48]. Buckley et al. observed that 16% of subjects (5 out of 32) had elevated levels of beta-tryptase, characteristic for anaphylaxis, while the levels of alpha-tryptase were normal [48]. In sera taken from 189 deceased subjects, McLean et al. recorded elevated tryptase (>11.4 g/L) in 57% of samples taken from the aorta, 58% of the femoral vein, and subclavian vein 30% [47]. Values above 110 ug/L collected from the aorta can, with a sensitivity of 80% and specificity of 92.1%, indicate anaphylaxis as the cause of death, but the diagnosis should not be made solely on the basis of this single test [47]. Elevated post mortem tryptase concentration does not have to be associated with death from anaphylaxis, but is

also observed in patients who died of myocardial infarction, asphyxia or trauma [12].

Marking of tryptase concentration in saliva may also be helpful in the diagnosis of food allergy. In a retrospective study, Rueff et al. took samples of saliva from 33 patients before the test and after 4 min of the first appearance of symptoms of anaphylaxis during oral provocation [49]. In 25 patients (75.8%) with a positive test result and symptoms of food anaphylaxis, significantly elevated levels of tryptase in saliva samples taken after 4 min of the first symptoms of anaphylaxis, were observed [49].

Tryptase is a highly specific marker of activation, number, location and secretion capacity of mast cells [10]. In healthy individuals, basic tryptase concentration remains stable for a long time [10]. It seems therefore very important not only to measure the one-off levels under conditions in which mast cell activation occurs (eg. anaphylaxis), but also to keep track of its dynamics of growth [10]. Unfortunately, tryptase is not an ideal biomarker of anaphylaxis, as its levels determined in the corresponding time window, remain low in 36–40% of patients with anaphylaxis (<11.4 ng/mL) or its dynamics of growth is not observed [10]. In addition, currently available methods of determining tryptase concentration, specify the total number of inactive forms of α- and β-tryptase and mature β-tryptase tetramers [10]. The ideal way to evaluate mast cells activation, would be the one that would measure only the concentration of mature, active β-tryptase tetramers [10]. Prieto-Garcia et al. showed that during the formation of mature β-tryptase tetramers, hFibrinogen fragments are formed, which could be a sensitive marker of mast cell activation in patients with anaphylaxis or mast cell activation syndromes [50].

Srivastava et al. observed that the level of tryptase in the course of an anaphylactic reaction is not specific to any particular cause of anaphylaxis and found a weak correlation between tryptase concentration and severity of anaphylaxis [51]. In addition, increased levels of tryptase were also observed in patients with only mild skin reactions, who did not meet the full criteria for a diagnosis of anaphylaxis [51]. The predictive value of elevated levels of tryptase (≥14 mg) in the acute phase in this study was 76.9% [51]. Interestingly, the majority of patients (total 171 people) were diagnosed with idiopathic anaphylaxis (50%), 28% – drug induced, 14% – caused by the consumption of foods with the remaining 8% – caused by exposure to allergens and mast cell activation syndrome [51].

Naturally occurring β-tryptase inhibitors are known; they were discovered in leeches and ticks, which can reduce the inflammatory reaction associated with tryptase, and skin itching caused by parasites [52].

Searching for inhibitors of human β-tryptase is very difficult; the molecules would have to be highly selective for this enzyme, inhibiting its activity in a reversible way and have adequate pharmacokinetic and pharmacodynamic properties such as, for example, the possibility of oral administration [52]. It should also be taken into account that the serine proteases, which include, among others, tryptase, determine the proper course of many important physiological processes, such as digestion, hemostasis, fibrinolysis, activation of the complement system, signal transduction and cell growth or regulation of the transport of ions [52].

3.3. Histamine

Histamine (2-{4-imidazole]-ethylamine) is a short-acting endogenous amine, involved in several physiological and pathophysiological processes [53]. Histamine is synthetized from L-histidine by L-histidine decarboxylase and is stored in the granules of mast cells and basophils, the main sources of histamine in the body [54]. Histamine is often considered the most important mediator of anaphylaxis. It is also involved in other inflammatory processes; it is a neurotransmitter; and increases the secretion of gastric acid. The granules of basophils and mast cells contain histamine [55]. It is present in histaminocytes in the stomach and in histaminergic neurons within the central nervous system. Histamine release could occur as a result of antigen-antibody reaction or direct damage to the membranes of mast cells caused by physical factors (pressure, cold). Certain drugs might also stimulate its secretion [55].

Histamine acts in multiple ways by stimulating receptors H1, H2, H3, H4 [55], belonging to the subclass of G protein-coupled receptors [56].

The human histamine receptor 1 is expressed in numerous cells including airway and vascular smooth muscle cells, endothelial cells, dendritic cells, monocytes, neutrophils, T and B cells, hepatocytes, chondrocytes, and nerve cells [57–59].

Stimulation of H1 receptor causes: contraction of smooth muscle (shortness of breath, abdominal pain) – the so-called H1 effect, increase in vascular permeability (hives, swelling, skin redness) and vascular extension (synthesis of nitric oxide (NO) by endothelium), stimulation of nerve endings (itching), and increased viscous mucus secretion [55]. Histamine H1 receptors mediate sensorineural signalling, vascular dilatation and permeability and airway smooth muscle contraction. They are involved in allergic rhinitis, atopic dermatitis, conjunctivitis, urticaria, asthma and anaphylaxis [60]. Through the H1-receptor, histamine contributes to regulation of cell proliferation and differentiation, hematopoiesis, embryonic development, regeneration, and wound healing and plays an important role in neurotransmission in the central nervous system (CNS) [60–63]. Histamine produced in neurons has anticonvulsant activity and contributes to regulation of vigilance (alertness and attention), cognition, learning, memory, and the circadian sleep-wake cycle, as well as to energy and endocrine homeostasis [60–63]. Through the H1-receptor, histamine increases antigen-presenting cell capacity, increases release of histamine and other mediators from mast cells and basophils, downregulates humoral immunity, and upregulates Th1 priming, Th1 proliferation, IFN-γ production, cellular adhesion molecule expression, and chemotaxis of eosinophils and neutrophils [61]. All above mentioned mechanisms could play an important role in the pathogenesis of anaphylaxis.

H2 receptors are expressed in gastric parietal cells, smooth muscle cells, neutrophils, eosinophils, monocytes, macrophages, dendritic cells, T and B cells, endothelial cells, epithelial cells and cells in cardiovascular and central nervous system [61,64]. Histamine H2 receptors are well known for their role in gastric acid secretion, and also exert immunomodulatory properties [53].

Stimulation of H2 receptor in the heart induces a positive inotropic and chronotropic reaction and dilates coronary vessels (unlike H1 receptor, which is responsible for their shrinkage) [55]. Simultaneous stimulation of H1 and H2 vascular endothelial receptors causes symptoms such as redness of the skin, headache, decrease in blood pressure [55]. This action on the vascular bed, causing it to expand and in effect: skin erythema; is called the H2 effect [55]. H2 receptor-mediated smooth muscle relaxation have been documented in vascular smooth muscle, uterus and in airway [65]. The activation of H2 receptor may result in inhibition of variety of functions within the immune system. H2 receptors have been shown to be involved in negative regulation of the release of histamine from mast cells and basophils [65]. H2 receptors also participate in the inhibition of antibody synthesis, T cell proliferation, cell-mediated cytolysis and cytokine production [66].

Considering the above mentioned effects of H2 receptor activation, one should expect its potential protective role in the pathogenesis of anaphylaxis.

Histamine H3 receptors are most abundantly present in the CNS and are implicated in sleep-wake disorders, attention-deficient hyperreactivity disorder, epilepsy, cognitive impairment and obesity [67,68]. H3 receptors are also expressed in neuroendocrine tissues such as enterochromaffin-like cells and adrenal cortex [69]. Extensive investigations have revealed that brain H3 receptors regulate the release of various neurotransmitters, such as acetylcholine, glutamate and GABA (gamma-aminobutyric acid) [70]. H3 receptors are found in the hypothalamus and their stimulation hinders the release of norepinephrine, this then contributes to shock [55].

Histamine H3 receptors have been identified on presynaptic terminals of sympathetic effector nerves that innervate the heart and systemic vasculature [71–73]. These receptors have been found to inhibit endogenous norepinephrine release from the sympathetic nerves [72]. H3 receptor activation would therefore be expected to attenuate the degree of shock observed during antigen challenge since compensatory neural adrenergic stimulation would be blocked [71–73].

In addition to inhibiting norepinephrine exocytosis from sympathetic nerve endings, selective H3R agonists attenuate carrier-mediated release of norepinephrine (NE) in both animal and human models of protracted myocardial ischemia [74]. Moreover, stimulation of H3 receptors is not associated with negative chronotropic and dromotropic effects (i.e., sinoatrial and atrioventricular nodal functions are unaffected) [74]. Because excess norepinephrine release can trigger severe arrhythmias and sudden cardiac death, negative modulation of NE release by H3R agonists may offer a novel therapeutical target points in the potential treatment of myocardial ischemia, also of that associated with Kounis syndrome (the pathogenesis of Kounis syndrome is described below) [74].

Discovered in the beginning of the twenty-first century, H4 receptors are located primarily in immunocompetent cells, such as: mast cells, eosinophils, monocytes, dendritic cells, T-lymphocytes and NK cells [75]. Their presence has also been demonstrated in spleen, thymus, intestine, kidneys, lungs, testis and bone marrow [75]. Histamine H4 receptors are currently under evaluation for immune-mediated disorders such as allergic rhinitis, asthma and pruritus [76]. The affinity of H4 receptor to histamine is much bigger than H1 receptor's [75]. H4 receptor's role in anaphylaxis lies in the intensification of the chemotaxis of eosinophils and mast cells and expression of adhesion molecules, mobilization and differentiation of monocytes, T_H1/T_H2 lymphocytes, and stimulation of cytokine and chemokine production by dendritic cells and T-lymphocytes [75]. In phase I and phase II of clinical trials, H4 receptor blockers were used in the treatment of asthma, allergic rhinitis, atopic dermatitis, histamine-induced pruritus or rheumatoid arthritis, which indicates its important role in the pathogenesis of inflammatory diseases [77].

Compared with H1 and H2 receptors, histamine displays high affinity for H4 receptors in humans (pKi 4.2, 4.3 and 7.8, respectively) [78].

Since during anaphylaxis the concentrations of histamine are high, all subtypes of histamine receptors are expected to be activated. Considering that histamine has low affinity (H1, H2) and high affinity (H3, H4) receptors, and the fact that anaphylaxis is associated with high plasma histamine, one should expect activation of all subtypes of histamine receptors.

It has been demonstrated in animal model studies that type 4 of histamine receptors (H4) play an important role in anaphylactic reaction to peanuts [79]. Mice allergic to nuts without H4 receptor had less severe gastrointestinal symptoms (diarrhea, inflammatory bowel disease) and fewer dendritic cells in the intestinal mucosa [79]. In addition, it was observed that when H1 receptor was blocked by loratadine and H4 receptors by their selective antagonist – JNJ7777120, animals allergic to nuts were being protected from the development of abdominal symptoms and the influx of dendritic cells to the intestinal mucosa was restrained [79]. These observations may provide a valuable basis for the development of therapeutic strategies that take into account H4 receptor blockade in treatment and prevention of anaphylactic reactions, especially in people allergic to peanuts.

Histamine has long being considered an important mediator of anaphylaxis [80]. Weiss et al. showed that aerosol administration of histamine induces bronchoconstriction in healthy volunteers, although the effect of histamine was much less potent than that of leukotrienes [81,82]. Intravenous administration of histamine in volunteers can reproduce many of the signs and symptoms of anaphylaxis, including cutaneous flushing, headache, airway obstruction, and transient hemodynamic changes, mainly represented by systemic hypotension, tachycardia, and increased left ventricular performance [83,84]. Studies with histamine receptors antagonists suggest that some of the systemic effects of histamine, including airway obstruction and tachycardia, are mainly mediated through the H1 receptor, whereas some others, including cutaneous flushing and headaches, seem to be mediated through both H1 and H2 receptors [83].

Although determining the concentration of tryptase seems to be the most useful diagnostic test in clinical practice to confirm anaphylaxis, some studies have shown that histamine is a more sensitive marker of anaphylactic reaction [85]. In a study by Lin et al. elevated histamine levels in plasma were observed in 42 out of 97 patients with anaphylaxis, while elevated levels of tryptase have been shown in only 20 [86]. Patients with elevated levels of histamine demonstrated symptoms such as hives, severe erythema, abdominal pain and wheezing, more often [86].

Histamine level in plasma increases within 5–10 min from the start of anaphylaxis and returns to its normal level within 30–60 min [2,10]. This rapid drop is caused by the decomposition of this mediator by N-methyltransferase, and diamine oxidase to N-methylhistamine and N-methylimidazole octane [10]. These metabolites are more stable and can be measured in plasma and urine within 30–60 min of an anaphylactic reaction, but their normal levels do not preclude the activation of mast cells, and false-positive results could be due to the consumption of foods rich in histamine [10].

3.3.1. Histamine and myocardial dysfunction

The effects of histamine on peripheral and coronary hemodynamics in man was studied by Marone et al. [87]. The authors have found that exogenous histamine causes significant transient hemodynamic changes, mainly systemic hypotension, tachycardia, and increased LV (left ventricle) performance [87]. These changes can be partly attributed to the related increase in sympathoadrenergic activity, although it cannot be excluded that histamine has some direct cardiac effect [87].

In a subsequent study, the effects of selective activation of histamine H1 receptors on coronary hemodynamics were examined in two groups: patients with atypical chest pain and normal coronary arteries and patients with vasospastic angina [88,89]. H1 receptor stimulation was achieved by infusing histamine intravenously for 5 min after pretreatment with cimetidine to antagonize the H2 receptors [88,89]. Heart rate was kept constant by coronary sinus pacing. In the first group mean aortic pressure and coronary vascular resistance (CVR) dropped, while coronary blood flow (CBF) and myocardial oxygen consumption remained unchanged during histamine infusion. No patient in this group developed angina during histamine infusion. By contrast, a percentage of the second group developed angina during histamine infusion (about 40%), with a decrease in CBF and an increase in CVR [88,89]. These findings suggest that stimulation of the H1 receptor in subjects

with normal coronary arteries reduces CVR, probably because of vasodilation of small coronary resistance vessels [88,89]. However, in some patients with vasospastic angina, H1 receptor activation can cause vasoconstriction of large-capacitance coronary arteries [88,89]. The results of these studies support the hypothesis that the endogenous release of histamine during anaphylactic reactions may result in coronary spasm in a subset of patients with vasospastic angina. Of importance, it has been reported that premedication with H2 receptor antagonist increases the risk of heart block in patients who develop anaphylaxis [90]. Studies have now started to clarify the role of H3 receptors in the cardiovascular system. Roberto Levi and collaborators have identified H3 receptors as inhibitory heteroreceptors in cardiac adrenergic nerve endings [91,92] suggesting a mechanism by which endogenous histamine can activate norepinephrine release in normal and ischemic conditions [93]. Accordingly, the presence of H3 receptors in human heart [91] suggests that these receptors might be directly and/or indirectly involved in anaphylactic reactions.

In the course of anaphylaxis, mediators from mast cells are released locally and in the systemic circulation [7]. Majority of these mediators has important cardiovascular actions [7]. Specifically, histamine induces coronary vasoconstriction, induces tissue factor expresssion and activity, and potentiates the platelet aggregatory response to adrenaline, 5-hydroxytryptamine, and thrombin [32]. Histamine can also induce intimal thickening and inflammatory cells modulation, i.e. it alters the activity of neutrophils, monocytes and eosinophils and causes proinflammatory cytokine production [7,94]. Moreover, histamine causes P-selectin upregulation and sensitized nerve endings in coronary plaques [7]. All neutral proteases (tryptase, chymase, and cathepsin D) released from mast cells can activate matrix metalloproteinases, which can degrade the collagen cap and induce plaque erosion and rupture [32].

More details on the role of tryptase in the pathogenesis of acute coronary syndromes are described in the previous chapter.

All pre-formed and newly synthesized inflammatory mediators released locally and pouring into systemic circulation can cause either coronary artery spasm which could progress to acute myocardial damage or immediate coronary thrombosis which constitute the main clinical manifestations of Kounis syndrome [7].

Kounis syndrome is defined as a hypersensitivity coronary disorder induced by various conditions, drugs, environmental exposures, foods and coronary stents [7]. Kounis syndrome is associated with allergic, hypersensitivity, anaphylactic and anaphylactoid reactions [7]. So far, three variants of this syndrome, including vasospastic allergic angina, allergic myocardial infarction, and stent thrombosis with occluding thrombus infiltrated by eosinophils and/or mast cells, were reported [94]. In addition to coronary arteries, it affects the cerebral and mesentheric arteries [7]. The principal clinical symptoms and signs of Kounis syndrome are always related to subclinical, clinical, acute or chronic allergic reaction accompanied by cardiac symptomatology [7]. The type I variant (coronary spasm) which is likely to represent a manifestation of endothelial dysfunction or microvascular angina, includes patients with normal or nearly normal coronary arteries without predisposing factors for coronary artery disease [7]. In this group of patients, the acute release of inflammatory mediators can induce either coronary artery spasm without increase of cardiac enzymes and troponins or coronary artery spasm progressing to acute myocardial infarction with raised cardiac enzymes and troponins [7]. The type II variant includes patients with culprit but quiescent pre-existing ateromatous disease [7]. In these patients, the acute release of inflammatory mediators can induce either coronary artery spasm with normal cardiac enzymes and troponins or coronary artery spasm together with plaque erosion or rupture manifesting as acute myocardial infarction [7]. The type III variant includes patients with coronary artery stent thrombosis in whom aspirated thrombus specimens demonstate the presence of eosinophils and mast cells [7]. This variant is also found in patients with stent implantation who died suddenly and histological examination of coronary intima or media and/or adventitia adjacent to stent revelaed infiltration by eosinophils and/or mast cells [7,95].

3.4. Platelet-activating factor (PAF)

Platelet-activating factor (PAF – platelet-activating factor, 1-*O*-alkyl-2-acetyl-sn-glycerol-3-phosphocholine) is a phospholipid mediator, which belongs to the family of biologically active compounds – alkylated phosphoglycerides [96–104]. PAF, discovered at the beginning of the 70 s by Benveniste et al. [105], affects target cells by activating a specific receptor coupled with G protein, which activates phospholipase C [103]. Results of *in vitro* studies demonstrate that PAF acts as an intra- and extracellular transmitter and plays an important role in intercellular interactions [98].

The most important enzyme regulating biological activity of PAF is PAF- acetylhydrolase (PAF-AH – acethylhydrolase-PAF), which converts active form of PAF into the inactive PAF – lysoPAF [106]. PAF-AH is present in plasma [106] and a number of tissues [107]. PAF- acethylhydrolase is present in plasma in the form of complexes with HDL and LDL cholesterol [108].

Apart from the enzyme operating outside the cell, two intracellular forms were also identified [109–111]. PAF-AH, apart from the platelet-activating factor, also induces degradation of oxidized phospholipids, and these may be attached to PAF receptors [112]; their participation in the formation of atherosclerotic plaques is implied [113].

PAF is present in plasma at very low concentrations – $10/^{-12}$ M, and its biological half-life is very short [20,114,115]. PAF is not stored, but quickly synthesized from choline-ether-phospholipids occurring in cell membranes, with the involvement of phospholipase A2 and acethyltransferase. PAF causes, among others, vasodilation and an increase in vascular permeability, bronchoconstriction; it has a strong chemotactic effect and induces the release of many cytokines [116]. This substance is produced by various cell types [117], in particular by inflammatory cells: monocytes/macrophages, mast cells, neutrophils, eosinophils, basophils, platelets, endothelial cells, Kupffer cells in the liver, and even sperms [97,114,116,118–120]. It has been shown that endothelial cells have the ability to synthesize PAF under the influence of a number of inflammatory mediators such as thrombin [121,122], angiotensin II [112], vasopressin [121], leukotrienes C4 and D4 [122], histamine [122,123], bradykinin [122,123], elastase [124], cathepsin G [124] and hydrogen peroxide [125], plasmin [126,127], IL-1α and −8 [128] and tumor necrosis factor – TNF-α [129,130]. Under certain conditions, upon stimulation, PAF may also be produced by cardiomyocytes [131]. The majority of cells having the ability to synthesize PAF also have suitable receptors [132–136]. *In vitro* studies have demonstrated that PAF potentiates aggregation, granule secretion, and generation of free radicals by leukocytes and their adhesion to endothelial cells [137,138]. In addition, PAF increases the permeability of endothelial cells [130,139], activates platelets [140], stimulates smooth muscle contraction: bronchial and intestinal [114,141–143] and uterus [144,145], is arrhythmogenic, has a negative inotropic effect on cardiomyocytes [140,146–149], can cause fainting in cardiogenic mechanism and hypertension in the portal system [114].

Mast cells – cells functioning as “controllers” in the immune system, and mediators such as histamine and PAF, play a major role in the pathogenesis of anaphylactic reactions, both observed in patients, as well as based on experimental models [150,151].

Recent studies, indicating the very important role of platelet-activating factor in an anaphylactic reaction, suggests that it might become the target point for new therapeutic strategies.

Results of studies on the animal model suggest that induction of PAF synthesis is an essential process in the development of anaphylactic reactions [150,152,153]. Furthermore, these observations indicate particularly important role of this mediator in increasing vascular permeability [150,152,153]. Increased expression of its receptor (PAF-R) on inflammatory and endothelial cells was observed in allergic diseases [116].

Studies on animal model have shown that recombinant PAF-acetylhydrolase plays a protective role and reduces mortality due to anaphylactic reactions, which confirms the important role of platelet-activating factor cascade in potentially life-threatening hypersensitivity reactions [150,154].

Vadas et al. observed increased concentrations of PAF in plasma during an acute allergic reaction in children and adults, which correlate with the severity of anaphylactic reactions [151]. It was detected that PAF concentration correlates very well with the severity of an anaphylactic reaction [151], even better than the concentration of histamine or tryptase [155]. In this study the percentage of patients with elevated levels of PAF was respectively: 20, 66,7 and 100% for steps 1, 2 and 3 on a scale of severity of an acute allergic reaction, while for histamine: 40, 57 and 70%, and tryptase: 0, 4, 8 and 60%. The authors also observed that the severity of anaphylactic reactions correlated with decreased activity of PAF-AH in plasma, and the concentration of PAF was inversely proportional to its activity. The activity of PAF-acetylhydrolase in plasma was significantly reduced in patients who died of anaphylactic reaction after eating peanuts, when compared to the control group [151]. It seems that low activity of PAF-AH can be genetically determined by the presence of alleles His92 [156].

In a study of 315 cases of anaphylactic reactions, Brown et al. have shown that low activity of PAF-AH is associated with severe course of anaphylactic reactions, but no correlation with the presence of two-phase reactions, concomitant diseases or any demographic factors (age, sex, race) was demonstrated [13].

Platelet-activating factor plays an important role in anaphylaxis caused by peanuts [157]. Studies on animal model demonstrated that PAF antagonists relieve the symptoms of food allergy to peanuts [157]. Administration of antihistamines or antileukotrienes was not effective in this case, but administration of PAF antagonists and antihistamines combined, significantly decreased the symptoms, more than administration of only the antagonists of platelet-activating factor [157]. Khodoun et al. showed that *in vitro* water extract of nuts (including peanut) but not from milk or eggs, activates the complement system in human and mouse serum [158]. C3a component is formed in result, which in turn stimulates basophils and macrophages to produce PAF and histamine [158]. Taking into account the fact that anaphylactic reactions to peanuts are IgE-dependent, an additional mechanism associated with the activation of complement, could potentially aggravate their course [158]. It is now known that anaphylaxis to peanuts is the most common cause of death from food-associated anaphylaxis in the United States, and its course is often dramatic [157].

There are many natural and synthetic PAF inhibitors. Rupatadine, a substance which is a potent inhibitor of histamine (H1) and PAF receptor, is also used in the treatment of allergic rhinitis and urticaria [159]. Recent studies indicate that the activity of various mediators, partially independent from each other, influences the severity of anaphylaxis. Results of studies conducted in animal models by Nagi-Miura et al. are worth noting in this regard. The authors proved that during a fatal anaphylactic shock induced in mice, co-administration of antagonists of H1 and H2 receptors, PAF receptors and serotonin prevents death in 80% of animals, while applying a single one of them is effective in 20% of cases at most [160]. *In vitro* studies conducted by Alevizos et al. demonstrated that PAF-stimulated release of histamine, interleukin-8, TNF, and P substance by human mast cells, is inhibited by rupatadine, while this was not observed after administration of diphenhydramine [161]. In a clinical study in patients with mastocytosis, a reduction of skin symptoms and tachycardia after administration of rupatadine was noted [162]. So far no reports were published on the effectiveness of rupatadine in anaphylaxis. On the basis of the above it can be assumed, however, that there are important theoretical reasons to consider this substance as a drug of choice in all types of anaphylaxis where oral H1-antihistamine is recommended [163]. This applies particularly to the prophylactic of recurrent episodes of idiopathic anaphylaxis [163]. A similar reasoning can be applied also in relation to people with a history of anaphylactic shock when its cause is known (eg. Hymenoptera stings) treated with an antihistamine because of allergic rhinitis [163]. Further research is needed, to verify this hypothesis.

3.5. Genetic markers of anaphylaxis

Although all of above discussed markers can be relatively easily measured in peripheral blood, however, sensitivity of the detection as well as the timing remain a challenge. Therefore, there is a need for identifying more “stable” markers that could help in prophylaxis and identifying persons at increased risk of anaphylaxis. To date, several genes have been associated with increased risk of anaphylaxis in clinical and experimental settings. Mutations of c-KIT being one of crucial genes regulating mast cell function were linked not only with mastocytosis (e.g. mutations in exon 17) but also with so called “idiopathic” anaphylaxis [164]. Interestingly, enhanced risk of anaphylaxis was found to be associated with aberrations of genes regulating innate immune responses. One of crucial controllers of innate immunity is NLR family, pyrin domain containing 3 (NLRP3) that regulates the forming of inflammasomes, the process which results in maturation of IL-1beta and IL-18. Hitomi and colleagues found that two NLRP3 SNPs (rs4612666 and rs10754558) were significantly associated with susceptibility to food-induced anaphylaxis [165]. Interestingly, these polymorphisms were also correlated with aspirin-induced asthma. Other associations with food-induced anaphylaxis were found by Gorska and colleagues that have found increased expression of gene for TRAF-4 (TNF receptor-associated factor 4) in mastocytosis patients with a hypersensitivity to food; and reduced for B3GAT1 (galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 1) in patients with anaphylactic reaction after Hymenoptera sting [166]. History of anaphylactic reactions was also linked to alterations within genes encoding interleukins crucial for regulating Th1/Th2 balance. IL4 single nucleotide polymorphisms: rs11740584, rs10062446 and rs2070874 were associated with penicillin-related anaphylaxis [167]. Similarly, two linked IL-10 promoter gene polymorphisms, $-819C > T$ and $-592\ C > A$ were demonstrated to be related with penicillin allergy in female patients [168].

4. Conclusion

As anaphylaxis can be a potential life-threatening condition, its rapid diagnosis and prompt initiation of an appropriate therapy, are crucial. The appropriate diagnosis of anaphylaxis can be facilitated by determining several markers which not only allow to confirm (or rule out) this disease, but can also be helpful in assessing the risk of repeated episodes as well as become the target point for developing new therapeutic strategies.

Conflict of interest

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