Aspirin-sensitive asthma due to diffuse neuroendocrine system pathology

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Abstract

Available clinical data on aspirin-sensitive asthma (ASA) indicate that ASA patients have certain disturbances in the nervous, endocrine, immune and other body systems. It has been found that such patients have a lower melatonin (MT) production in daytime, a pathology of the platelet membrane-receptor complex, and a pathological response to exogenic MT and acetylsalicylic acid. A hypothesis has been suggested in which ASA is considered as apudopathy caused by dysfunction of MT-producing cells. The decreased MT production and the disturbed cell sensitivity to MT lead to pathological changes in individual organs and functional systems. As a result, there is an enhanced lipid peroxidation, an excessive production of reactive oxygen radicals, and a reduced inhibitory action of MT on the 5-lipoxygenase and NO-synthase activities. The lower MT content also results in an intense aggregation of platelets, activating these cells and increasing the production of leukotrienes and nitric oxide. These changes disturb the pulmonary microcirculation, causing the bronchial obturation syndrome even in patient who do not take aspirin or other nonsteroidal anti-inflammatory drugs. The lower basic production of MT is also responsible for a lower content of its metabolite – endogenic acetylsalicylic acid, thereby increasing the sensitivity of melatonin-producing cells, in particular of platelets, to this acid. So, even minimal aspirin doses inhibit the activity of COX-1, which shunts the already abnormal metabolism of arachidonic acid. This, in turn, leads to a greater production of leukotrienes and, hence, to a severe course of the disease.

This hypothesis has become the basis for a new pathogenetic approach to the treatment of ASA patients by correcting the melatonin content with peptide bioregulators – the epiphysis extracts – Epithalamin and Epiphamin.
Aspirin-sensitive asthma (ASA) occurs in 20% of patients with bronchial asthma and is tending to increase its rate [1, 2]. Its characteristic symptom is intolerance to aspirin and other nonsteroidal antiinflammatory drugs (NSAID$_S$), which is manifested as acute asthma attack, often with recurrent polyposis rhinosinusopathy, with special emphasis on its pathogenesis and effective therapy [3]. Since the attempts to prove an allergic nature of this type of asthma have failed [4, 5, 6], a hypothesis has been put forth that ASA is due to an enhanced production of leukotrienes, which cause a persistent and intense contraction of the bronchial smooth muscles, to edema, eosinophils infiltration of the bronchial tree, and mucous hypersecretion [7, 8].

The high production of leukotrienes is attributed by some researchers to LTC$_4$ synthase hyperexpression [9] and by others to the inhibition of endogenic PGE$_2$ synthesis, which controls the leukotriene synthesis in the absence of NSAID$_S$ [10]. However, this hypothesis explains only the mechanism of aspirin-induced bronchoconstriction but fails to account for the disease gravity, its rapid progress, and the addiction to glucocorticoid hormones of even those patients who do not take aspirin or other NSAID$_S$.

Our clinical and laboratory studies of 133 ASA patients and 143 aspirin-tolerant (ATA) patients indicate that the former exhibit nervous, endocrine, immune and other functional disturbances prior to the asthmatic syndrome [11, 12]. The ASA patients show early indications of psychological disorders, manifesting themselves as alarm-depressive or asthenoneurotic syndromes. The disease origin in 18.3% of the patients was found to be associated with a psychological stress, which provoked an acute recurrent asthmatic syndrome in 78.6% of ASA patients.

An early symptom of immune disturbances in the ASA patients examined was the tendency for developing benign tumours. For example, 71.1% of them had polyposis rhinosinusopathy, which was diagnosed in 30% of these patients before the appearance of the first asthmatic attacks. Fibromyoma of the uterus was identified in 36% of the female patients. The ASA patients showed a lower resistance to viral infections, early inflammatory processes, as well as mycogenic, pollen, dust, food, epidermal, and drug sensitization. It was only in 28% of the patients that the first asthmatic attack was provoked by a dose of acetylsalicylic acid or NSAID$_S$. The asthmatic syndrome often developed for several months after the vaccination. Besides, 85.7% of the ASA patients showed a certain correlation between bronchial asthma and an acute respiratory viral infection, starting at the age of 16.

We also identified early endocrine disturbances in the ASA patients. For example, 25.9% of the examined females had a disordered menstruation and premature delivery; the menopause in this group of patients started at the age of 42–48. The exacerbation of the asthma course was in the second phase of the menstruation in 50% of young females. Besides, every fifth patient had problems with the thyroid gland, and glycometabolism was often abnormal with a tendency for hyperglycemia and a lower enzymatic liver activity. Chronic gastritis or ulcer were found in 35% and biliary duct pathology in 37% of the ASA patients. As for the blood-forming system, we recorded a reduced proliferation of the stem cells towards erythropoiesis and granulocytopoiesis with enhanced eosinophilopoiesis and megakaryocytopoiesis.

The cardiovascular system of ASA patients is characterized by a neurocirculatory hypotonic distonia and early indications of the varicosity. An increased amount of platelets, disturbances in the lung microcirculation, and polyposis rhinosinusopathy of the edematous type are indicative of profound disorders in the platelet-vascular hemostasis.

The first clinical disorders in the respiratory system are observed in the period of hormonal changes in the body as a rule. Asthma attacks in adult patients manifest themselves in the third and fourth decades of life in women and in the fourth and fifth decades in men; in children this usually happens at the prepubertate age. Immediately after the first attacks, the disease shows an severe and progressive course with a rapid development of addiction to glucocorticoids. ASA patients suffer from obstructive ventilation disorders in the distal bronchi, with an incomplete relaxation of the obstruction following β-adrenergic inhalation [13, 14]. There is no clear boundary between successive asthma attacks, but there is the sensation of a permanent chest discomfort, when the effectiveness of common broncholytic drugs is reduced. One can observe early signs of capillary circulation disorders: the lung scintigraphy registers vast areas of totally cut-off microcirculation in every second patient [15, 16, 17].

Thus, the clinical records of the disease show that ASA involves the abnormality of all functionally important systems. This can occur only if the diffuse neuroendocrine (APUD) system is affected, in particular, if there are disturbances in the production of melatonin, which plays an important role in the regulation of biological rhythms, in the coordination of intercellular relations, and in the integration of the activity of all functional systems of the body [18, 19, 20].

The results of our investigations have revealed a low basic MT production, as evidenced by a lower daytime excretion of urine aMT$_6$. We have found that the changes in the daytime MT production in ASA patients are unrelated to the activity of N-acetyltransferase but are likely to be associated with the condition of MT-

ABBREVIATIONS:
ASA aspirin-sensitive asthma
NSAID$_S$ nonsteroidal antiinflammatory drugs
ATA aspirin-tolerant asthma
APUD diffuse neuroendocrine system
MT melatonin
aMT$_6$ 6-sulphatoxymelatonin
SNAS 5-sulphatoxy-N-acetylserotonin
NO nitric oxide
COX-1 cyclooxygenase 1
producing cells, especially of platelets, in the APUD-system [21, 22].

The synthesis of MT is known to decrease considerably in light. In daytime, the MT production in the body is likely to be determined by the state of the APUD cell structures, especially of platelets, which are a basic peripheral storage of serotonin [19, 23, 24]. This conclusion is supported by the data showing that platelets produce not only MT itself but also one of its metabolites – 5-sulphatoxy-N-acetylserotonin (SNAS). Like aMT6s, SNAS is excreted with urine but it does not have a diurnal periodicity [25]. It is known that the serotonin uptake by platelets is greatly reduced in ASA patients [26]. This may lead to a reduction in their MT synthesis, determining the low daytime aMT6s excretion with urine. It appears that ASA patients show a high correlation between the MT production and the platelet functional activity [21].

We have studied the response of platelets from ASA patients to the addition of exogenic MT in vitro. It is found that the platelets show a pathological response manifested as an activation of the first aggregation phase on addition of minimal MT concentrations. This is due to the opening of the same receptor-operated channels for calcium and/or Ca2+ mobilization from the intracellular stores [21, 27, 28].

The platelet response to the addition of acetylsalicylic acid in vitro, like in the case of MT addition, is manifested as a change in the first phase of ADP-induced platelet aggregation, indicating a pathology of the membrane-receptor complex and a disorder of the Ca2+ cell homeostasis [13, 29].

Platelets of ASA patients are always activated. This may increase the cytoplasmic Ca2+ concentration and enhance the metabolism of membrane phospholipids, stimulating the platelet aggregation, which is accompanied by the release of a variety of biologically active substances. This, in turn, entails a whole cascade of reactions, leading eventually to the development of bronchoconstriction, vasospasm, mucous edema of distal bronchi, interstitial lung edema, the bronchial obturation syndrome, and disturbances in the ventilation-perfusion balance.

The observation of systemic changes in the homeostasis of ASA patients has been supported by our data on decreased contents of thromboxane A2 and prostacyclin in the blood plasma. It seems quite likely that a great contribution to the genesis of this effect is made by the low MT production by both platelets and vascular endothelium [30].

Normally, the production of prostacyclin by endothelial cells goes in parallel with that of nitric oxide. Our results show, however, that the nitric oxide content in ASA patients is increased due to its rise at night, and there is no correlation with the daytime MT production characteristic of normal subjects [30, 31]. It is possible that the greater NO production is due to the activation of constitutive NO-synthases because of the lack of MT control of their activity. The excessive NO contents increase the production rate of peroxynitrite which damages the vascular endothelium, stimulates the aggregative activity of platelets, cancels the inhibitory effect of NO and prostacyclin on the platelet aggregation, and reduces the sensitivity of the vascular endothelium to vasodilator agents. The result is the disturbance of microcirculations in the lungs and other organs and tissues.
The low MT production in ASA patients also determines the characteristically fast development of addiction to glucocorticoid hormones. Our investigations have shown that the cortisol level in the blood serum does not change in the morning. However, a single dose of dexametasone decreases the cortisol content drastically (by over 90%). The absence of correlation, typical of normal and ATA subjects, between the cortisol levels prior to and after the dexametasone dose together with the low level of MT production indicates a disturbed epiphyseal regulation of the hypothalamo-pituitary-adrenal axis function. Under the conditions of permanent stress, this may promote the development of a secondary insufficiency of adrenal function in ASA patients. [32, 33].

Therefore, aspirin-sensitive asthma should be regarded as apudopathy with the underlying pathology of MT-producing cells, i.e., as a defect of their membrane-receptor organization resulting in lower MT production. Having been synthesized by APUD-cells in various organs, MT enters the blood circulation, where it forms specific conformational bonds with hemoglobin to be transported to all organs and tissues, thereby providing the regulation of every organ function and the coordination of intra- and intercellular processes [34]. The lower basic MT in ASA patients and the abnormal cell sensitivity to MT lead to pathological changes in the body’s organs and systems (Fig. 1).

Among other consequences of low MT production are the enhancement of lipid peroxidation, the formation of excessive amounts of highly reactive O₂ radicals, and the reduced MT inhibitory effects on the activities of 5-lipoxygenase, NO-synthase, and platelet aggregation. This may be the reason for the overproduction of cysteinyl-leukotrienes, NO and platelet’s activation (Fig. 2). These processes disturb the lung microcirculation, leading to a bronchial obturation syndrome even in patients who do not take aspirin or other NSAIDs. The lower basic MT also leads to a decreased production of its metabolite – endogenic acetylsalicylic acid [35], – thus increasing the sensitivity of MT-producing cells to it, in particular, of platelets. The result is that even minimal aspirin doses inhibit the COX-1 activity, shunting the already disordered metabolism of arachidonic acid towards a more intensive production of leukotrienes, followed by life-threatening attacks of asthma.

The hypothesis we have described serves as a basis for a new pathogenetic approach to the treatment of ASA conditions by correcting the MT content in the body. The use of peptide bioregulators – the epiphyseal preparations of epithalamine and epiphamine – increases the MT contents in daytime and at night and improves the patient’s condition and life quality [36].

To conclude, aspirin-sensitive asthma is due to the pathology of melatonin-producing APUD-cells. This is a defect of their membrane-receptor complex and a low MT production rate. In combination with a distorted cell reception to MT, this leads to pathological changes in individual organs and functional systems, followed by the development of the asthmatic syndrome.