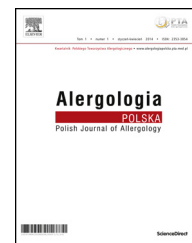


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Review / Praca pogładowa

Adipose tissue as a potential source of hormones and cytokines involved in asthma pathogenesis



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ABSTRACT

Asthma and obesity are chronic inflammatory diseases affecting millions of people worldwide. Numerous epidemiological data have revealed increased adiposity as a potential risk factor for severity and incidence of asthma. In addition, obesity is not only risk factor for asthma but is also related to its poor control. Despite the mechanism underlying obesity–asthma relation is not fully understood, it has been proposed that the common inflammatory mechanism plays a crucial role in determination of this relation. Adipose tissue is referred as extremely active endocrine organ secreting numerous hormones and cytokines that regulate immune responses and metabolism. In the lean state, the high levels of anti-inflammatory adipokines such as adiponectin as well as low levels of pro-inflammatory adipokines i.e. leptin, and pro-inflammatory cytokines such as TNF- α , IL-8, IL-6 are secreted by adipose tissue. On the other hand, in the obese state, hypertrophic adipocytes and activated macrophages produce decreased level of adiponectin and increased levels of pro-inflammatory adipokines and cytokines leading to “metabolic inflammation”. It may be possible that these obesity-related pro-inflammatory adipokines may be associated with airway inflammation in obesity-related asthma. In the current review, we summarized the recent knowledge concerning possible molecular mechanisms mediating the relation between obesity and asthma.

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Introduction

Obesity is referred as inflammatory, multifactorial diseases with increased prevalence over the recent years. WHO factsheet reported that approximately 300 million women and 200 million men are obese; more than 1 billion adults

are overweight (39% of adults [aged 18 and over] are overweight while 13% of adults are obese) worldwide. Genetic, environmental and socio-economic factors contribute to development of obesity commonly defined as body mass index (BMI) ≥ 30 kg/m² [1–3]. Nowadays, it has been estimated that approximately 38% of adults in the United States suffering from asthma are obese [4]. Asthma is

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a heterogeneous, chronic, inflammatory airways disorder characterized by hyper-responsiveness of airways leading to reversible obstruction of airflow in the lungs, and recurrent widespread episodes [5]. The prevalence of obesity has increased dramatically over the last decades and its association with asthma is being increasingly recognized. Moreover, increased healthcare utilization, worse control of asthma and quality of life have been observed in obese asthmatics as compared to non-obese asthmatics. Thus, the obesity has been also reported as risk factor for development of asthma and comorbid condition associated with more severe asthma phenotypes [6, 7]. Activation of pro-inflammatory signaling pathway, altered production of cytokines, elevated acute-phase reactants identifying low-grade systemic inflammation that is associated with obesity [8]. Adipocytes secrete over 50 different adipokines contributing to inflammatory balance [9]. Unfortunately, the molecular mechanism driving relation between obesity and asthma is still not fully understood. Some literature evidence suggest that changes in the levels of hormones and cytokines derived from adipose tissue may be connected with obesity-asthma pathomechanism. In the lean state, adipose tissue is able to produce increased levels of anti-inflammatory adipokines i.e. adiponectin and decreased levels of pro-inflammatory cytokines including tumor necrosis factor α (TNF- α), IL-8, IL-6 and pro-inflammatory adipokines i.e. leptin. In the obese state, activated macrophages and hypertrophic adipocytes are able to secrete high levels of pro-inflammatory cytokines and adipokines as well as low levels of adiponectin. In addition, increasing evidence suggest that upregulated adipokines i.e. leptin in obesity might be also involved in numerous obesity-independent inflammatory diseases [10, 11].

Better understanding of the molecular mechanism responsible for obesity-asthma relation may be a basis for development of new therapies in treatment of obesity-related asthma in the future. In the current review, we summarized the evidence and data concerning molecular mechanisms of obesity-asthma relation.

Adipose tissue as endocrine organ

The term of “adipose tissue” – a metabolically dynamic organ; refers to brown adipose tissue and white adipose tissue (WAT). Brown adipose tissue is found at birth and almost does not exist in adult humans. Its role is associated with thermogenesis – heat production [12]. In the human body, the majority of adipose tissue comprises WAT containing adipocytes as well as other types of cells i.e. fibroblasts, macrophages, endothelial cells, lymphocytes and vascular smooth muscle cells. The sources of adipocytes may be also lungs, bone marrow and blood vessels adventitia. Adipokines – a protein mediators; are secreted by adipocytes, macrophages, peripheral blood mononuclear cells, endothelial cells as well as bronchial and alveolar epithelial cells. Notably, adipose tissue secretes numerous cytokines (i.e. TNF- α , IL-6) and adipokines (i.e. adiponectin, leptin) having an synergic, adverse effect on the airways.

Because of the discovery of adipose tissue ability to secrete hormones and cytokines, its role has gained importance [12]. Adipose tissue participates in the complex network of paracrine, autocrine and endocrine signals involved in the regulation of cell functions that have impact on the response of immune system and various physiological processes. Thus, WAT may be defined as a highly active endocrine tissue [13] that possess a pleiotropic nature – starting from its ability to secrete numerous hormones, enzymes, growth factors, cytokines, matrix proteins and complement factors; finishing with theirs receptors expression involved in the regulation of many physiological processes such as energy expenditure, food intake, immunity, blood pressure and metabolism homeostasis [14, 15]. Fig. 1 shows some of WAT-secreted proteins both in conditions of hypertrophic and normal volume adipocytes.

Both macrophages and adipocytes are involved in the innate immune response: macrophages secrete chemokines

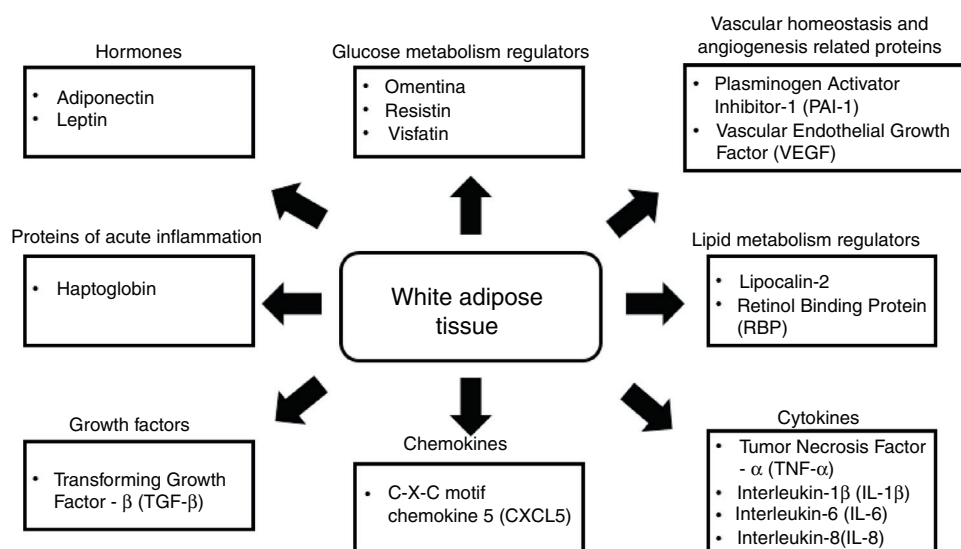


Fig. 1 – WAT-secreted proteins both in conditions of hypertrophic and normal volume adipocytes

and cytokines, as well as kill pathogens whereas adipocytes are able to neutralize pathogens and modulate inflammatory state [8]. Thus, WAT is not only an energy storage site, but also regulator of many pathological processes in the human body [9].

The results of experimental studies suggest differences in secretion and synthesis of adipokine between subcutaneous and visceral adipose tissue that are characterized by unique profile of adipokine production. In the visceral tissue, higher levels of PAI-1 and IL-6 have been identified. On the other hand, the higher levels of adiponectin and leptin have been observed in the subcutaneous tissue [16].

Adipokines and asthma

Adipokines (adipocytokines) – a components of adipose tissue such as adiponectin, resistin, leptin and visfatin; are protein mediators secreted by macrophages and adipocytes. In the human body, adipokines may act as both hormones – effect on energy balance; and cytokines – effect on inflammatory responses and immune functions [11, 17].

Adiponectin

Adiponectin (adipocyte complement-related protein) is a 30 kDa protein abundantly secreted and produced by adipose tissue. Adiponectin – insulin sensitizing hormone is also produced by airway epithelial cells [18] and adipocytes [19]. Its receptor is expressed on human smooth muscle cells [20], chondrocytes [21], human macrophages [22] and human airway epithelial cells [18]. Hypoxia, oxidative stress, TNF- α , IL-6 inhibit its adipocytes-related production [23, 24]. Anti-inflammatory effects of adiponectin is widely recognized [25, 26]. Adiponectin induces IL-1 receptor antagonist, IL-10 by human macrophages, monocytes and dendritic cells [27] as well as inhibits nuclear factor kappa B (NF- κ B)-dependent production of pro-inflammatory molecules i.e. interferon gamma (IFN- γ) and TNF- α in human macrophages [27, 28]. Miller et al. observed adiponectin dependent enhancement of pro-inflammatory IL-8 synthesis in airway epithelium of human [18]. Interestingly, several studies identified pro-inflammatory role of adiponectin by activating pro-inflammatory transcription factor, NF- κ B in monocytic cell lines [29] but NF- κ B is inhibited in endothelial cells [30]. In murine model, decreased serum level of adiponectin during pulmonary reaction has been observed [31].

Some studies have shown no correlation between adiponectin and asthma [35]. Several studies have identified the relation between adiponectin and asthma such as decreased level of circulating adiponectin in female asthmatics [32–34]. High serum level of adiponectin seems to reduce the risk of asthma development in women [33]. Moreover, positive correlation has been revealed between adiponectin serum level and improvement of asthma control [36]. The attenuation of airway hyper-responsiveness and allergic airway inflammation have been found after treatment with adiponectin in mice, identifying its protective properties against asthma [31]. Interestingly, Sood et al. observed more severe

asthma effect of adiponectin in male patients [36]. It has been also proposed that adiponectin may have both pro-asthmatic and anti-asthmatic effects in various groups of patients.

The majority of clinical studies' results have revealed decreased adiponectin levels as compared to controls [37]. But it is still not fully clarified whether the level of adiponectin is modulated only in obese-related asthmatics [31, 38–41]. Some studies identified that the levels of adiponectin did not differ in non-obese patients with asthma as compared to controls [31, 35]. The lower serum level of adiponectin in obese patients with asthma as compared to controls has been also found. Adiponectin and BMI may be highly related [42].

The level of adiponectin in obesity-related asthmatics is decreased as compared to lean asthmatics and non-obese asthmatic. Lean asthmatics also have decreased levels of adiponectin in comparison to obese or overweight asthmatics [43]. It has been proposed that the lower adiponectin level is related to uncontrolled asthma and may be also used as indicator of asthma [39]. However, its role in regulation of inflammation in asthmatic patients is still explored [43]. In addition, some studies also proposed the adiponectin as an indicator of asthma phenotype and progression based on analysis of resistin/adiponectin and/or leptin/adiponectin ratio [43, 44]. Both lung and airways epithelial cells are a potential target for adiponectin. Decreased IL-10 production and proliferation have been observed in epithelial A549 cell line [26]. Moreover, lower adiponectin levels have been also observed in OVA-challenged mouse model [39]. Increase of pulmonary vascular remodeling and allergic airway inflammation have been shown in murine model of acute asthma (OVA aerosol and OVA immunization with alum adjuvant challenges) [45]. The role of S1P in modulating ACRP30 action by stimulation of serum protein levels and its receptor has been also studied [39]. The treatment with recombinant adiponectin decreases S1P-induced hyper-responsiveness as well as inflammation. Some data support the modulatory role of adiponectin in pulmonary vascular remodeling and allergic inflammation in chronic asthma model [45]. However, the protective effect of adiponectin via adiponectin receptors in asthma is still not fully clarified. The role of adiponectin in pathogenesis of asthma in normal weight people should be further studied.

Leptin

Leptin is a 16 kDa protein expressed in human alveolar epithelial cells, bronchial smooth muscle cells, macrophages and alveolar type II pneumocytes [46–48]. It is involved in mediating signals via some intracellular pathways i.e. mitogen-activated protein kinases (MAPKs), p38 phosphatidylinositol 3 kinase (PI3K), Janus kinase 2 (JAK2)/-signal transducer, extracellular-signal regulated kinase (ERK) and activator of transcription 3 (STAT3) [49].

The role of leptin is related to not only the energy metabolism and appetite control via the central nervous system, but also regulation of inflammatory processes as well as both adaptive and innate immunity [50]. Leptin elevates the production of some pro-inflammatory cytokines

i.e. IL-6, IL-12 and TNF- α in macrophages and monocytes [51]. Moreover, it also induces neutrophils chemotaxis and oxidative stress via production of reactive oxygen species as well as inducible nitric-oxide synthase leading to modulation of the function and activity of neutrophils. Leptin also enhances natural killer cells activity and promotes phagocytosis in macrophages [52-54]. Thus, leptin is a pro-inflammatory adipokine.

Several studies have identified the association between level of serum leptin and asthma in human, especially in obese children and premenopausal women [41, 55, 56]. The level of leptin is higher in patients with asthma and it may be related to its role in the pathogenesis of asthma. In addition, the severity of asthma symptoms may be associated with serum level of leptin in asthmatics. In leptin-deficient mice, the exogenous leptin administration may elevate serum levels of allergen specific IgE and airway hyper-reactivity highlighting the role of leptin in asthma. The allergen inhalation has shown no effect on serum concentration of leptin in patients with mild atopic asthma [47]. Moreover, leptin increases the secretion of vascular endothelial growth factor (VEGF) from smooth muscle cells of airways and may have impact on airway remodeling, angiogenesis as well as muscle proliferation [20].

Many studies have confirmed the role of leptin in the pathogenesis of asthma [57]. On the contrary, several studies have shown no relation between circulating level of leptin and asthma [35, 58, 59]. Thus, the results of studies regarding the correlation between leptin and asthma in obese patients are still controversial.

Resistin

Resistin (FIZZ3 – “found in inflammatory zone”) is a member of resistin-like molecules family [60]. In the human body, its source is macrophages and adipose tissue suggesting its role in inflammation [61]. Pro-inflammatory cytokines i.e. TNF- α , IL-1 and IL-6 induces the expression of resistin gene and resistin modulates the expression of these pro-inflammatory cytokines, thus enhances its activity by a positive feedback [62, 63]. In human cells, a toll-like receptor 4 (TLR4) acts as receptor for pro-inflammatory activities of resistin whose may be intracellularly transmitted via NF- κ B signaling pathway [64, 65]. Because of decreased [58], increased [66, 67] or unchanged [68] levels of circulating resistin observed in asthmatics as compared to controls, its role in asthma is still not fully understood. Kim et al. observed negative correlation between bronchial hyper-reactivity and resistin pointing to its protective role directed against asthma [58]. On the contrary, resistin has been related to asthma severity in steroid-treated asthmatics [69]. It has been also observed that high levels of leptin are related to more sensitive asthma suggesting that relation between asthma and leptin is not limited to occurrence of obesity. In addition, resistin has been proposed as a marker of steroid-sensitive phenotype of asthma because of its high level enhancement of anti-inflammatory effect of glucocorticoids [70]. Resistin/adiponectin ratio is elevated in obese asthmatics and is related to more severe diseases. Both resistin and resistin/

adiponectin ratio may have negative effect on lung function and it may be a potential therapeutic target for obese asthmatics [44].

Visfatin

Visfatin is a 52 kDa protein expressed in visceral adipose tissue, circulating in high levels in obese patients, especially in children [71, 72]. However, unchanged [73] as well as decreased [74] levels of visfatin have been observed in obese patients as compared to non-obese patients and controls. Due to visfatin function as an enzyme, a cytokine and a growth factor as well as its role in lipid metabolism and regulation of glucose metabolism and inflammation, it is reported as a pleiotropic protein [75]. Visfatin plays an important role in inflammation and its upregulation is related to chronic low-grade inflammatory state development [11, 76]. Pro-inflammatory cytokines i.e. IL-6, IL-1 β and TNF- α and also lipopolysaccharide (LPS) induce visfatin expression in mammals [77]. Moreover, visfatin itself may promote the production of IL-6, IL-1 β and TNF- α via stimulation of MEK-1 and p38 MAPK pathways [78]. The correlation between low serum level of visfatin and atopic asthma in school children has been also observed [79]. Magrone et al. found increased serum levels of visfatin with BMI values in asthmatic children [80]. The pro-inflammatory role of visfatin in asthma development has been proposed due to its ability to secrete pro-inflammatory cytokines [81]. Thus, literature data support pro-inflammatory visfatin properties.

Conclusion

Numerous studies have shown the role of adipokines in the pathogenesis of asthma. Some of results are inconclusive and further studies are needed to determine the role of adipokines in asthma-obesity relation. However, it is possible that adipose tissue derived molecules may play a crucial role in phenotypes of asthma. To summarize, adipokines may play a role in a small part of asthma pathogenesis. Genetic, hormonal, epigenetic, developmental and mechanical effects of obesity may also be involved in severity and prevalence of asthma in obese asthmatics.

Conflict of interest/Konflikt interesu

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Ethics/Etyka

The work described in this article have been carried out in accordance with The Code of Ethics of the World Medical

Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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