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Review Article

Obesity-induced asthma: Role of free fatty acid receptors

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ABSTRACT

Obesity is a major risk factor for the development of asthma, and worsens the key features of asthma including airway hyperresponsiveness, inflammation, and airway remodeling. Although pro- and anti-inflammatory adipocytokines may contribute to the pathogenesis of asthma in obesity, the mechanistic basis for the relationship between asthma and obesity remains unclear. In obese individuals, the increased amount of adipose tissue results in the release of more long-chain free fatty acids as compared to lean individuals, causing an elevation in plasma long-chain free fatty acid concentrations. Recent findings suggest that the free fatty acid receptor 1 (FFAR1), which is a sensor of medium- and long-chain free fatty acids, is expressed on airway smooth muscle and plays a pivotal role in airway contraction and airway smooth muscle cell proliferation. In contrast, FFAR4, which is a sensor for long-chain *n*-3 polyunsaturated fatty acids and also expressed on airway smooth muscle, does not contribute to airway contraction and airway smooth muscle cell proliferation. Functional roles for short-chain fatty acid receptors FFAR2 and FFAR3 in the pathogenesis of asthma is still under debate. Taken together, adipose-derived long-chain free fatty acids may contribute to the pathogenesis of asthma in obesity through FFAR1.

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1. Introduction

Obesity is a major public health problem. According to the World Health Organization, more than 650 million adults are obese, and the worldwide prevalence of obesity nearly tripled between 1975 and 2016 [1]. Obesity is regarded as a risk factor for coronary heart disease, hypertension, type 2 diabetes, and atherosclerosis. In addition, recent evidence indicates that obesity is significantly associated with asthma [2]. Asthma symptoms in obese individuals tend to be more severe and do not respond as well to conventional pharmacological treatment such as corticosteroids and β_2 adrenoceptor agonists [3]. It was also reported that the majority of patients with severe or difficult-to-control asthma are obese [4]. Obesity worsened the key features of asthma including airway hyperresponsiveness, inflammation [5,6], and airway remodeling [7,8]. However, the mechanistic basis for the relationship between obesity and asthma is poorly understood. Epidemiological studies have suggested that a high-fat diet increases the risk of asthma [9,10]. High-fat diets elevate plasma free fatty acids levels, and suppress β_2 adrenoceptor agonists-induced bronchodilatory effect in asthmatic patients [11]. In obese individuals, plasma free fatty acids levels are chronically elevated due to an increased release of free fatty acid from enlarged adipose tissues [12]. Therefore, it is conceivable that increased serum free fatty acid levels in obese individuals could contribute to the pathogenesis of obesity-induced asthma. Recently, several orphan G-protein-coupled receptors (GPCRs) were identified as receptors for free fatty acids [13]. Interestingly, these free fatty acid receptors are expressed on airway structural cells including airway smooth muscle and epithelial cells, and play pivotal roles on pathogenesis of asthma.

In this review, we discuss the relationship between obesity and asthma, particularly focusing on the role of free fatty acids and their receptors on the pathogenesis of obesity-induced asthma.

2. Obesity-induced asthma

2.1. Epidemiology

In 1999, Camargo et al. first reported prospective data linking obesity with a risk for asthma [14]. Now, it is well recognized that obesity increases the prevalence and incidence of asthma in both adults and children. Epidemiological studies have shown that obese individuals with a body mass index (BMI) of >30 kg per m^2 have a

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92% increased risk of asthma [15]. Obese individuals with asthma are 5-fold more likely than lean patients with asthma to be hospitalized for an asthma exacerbation [16]. Many obese subjects with asthma have difficulty controlling their asthma with maintenance pharmacological therapies, and they exhibit increased use of rescue therapies [3]. Corticosteroids are also less effective in obese than non-obese subjects with asthma [17]. Obese subjects are more likely to have asthma-related hospitalizations compared with non-obese subjects [16].

Recent studies have suggested that obese asthmatic patients are subdivided into at least two distinct clinical phenotypes, those with early-onset allergic (EOA) asthma (T_H2-high), and those with late-onset non-allergic (LONA) asthma (T_H-2 low) [4,18]. EOA obese asthmatics have pre-existing allergic asthma that is complicated by obesity, whereas LONA obese asthmatics develop asthma symptoms as a consequence of obesity [3,18]. In LONA obese asthmatics, there is often little airway inflammation. When LONA obese asthmatics lose large amounts of weight after bariatric surgery, their degree of airway closure is significantly reduced, whereas closure in those with EOA obese asthmatics remains unchanged [18]. However, specifically tailored pharmacotherapeutic approaches for obese asthmatics have never been identified. For example, the oral anti-diabetic drug pioglitazone, which could be efficacious in the treatment of obesity-induced asthma through its metabolic effects on adipose tissue, has limited efficacy in the treatment of poorly controlled asthma in obese patients [19].

2.2. Biological mechanisms linking obesity and asthma

2.2.1. Mechanical and neuronal factors

Obesity is associated with excess fat on the anterior chest wall which lowers lung compliance and tidal volume. Several groups have suggested a plausible explanation that breathing at low lung volumes results in increased airway hyperresponsiveness [20]. Consistent with this hypothesis, increased airway hyperresponsiveness was observed in genetically obese mice [21]. In addition, there are changes in the neurological control of airway smooth muscle tone through the cholinergic signaling pathways in obesity [4]. Increased vagally mediated bronchoconstriction in obese rats is associated with loss of inhibitory M2 muscarinic receptor function on parasympathetic nerves [22]. Similarly, decreasing parasympathetic tone genetically or pharmacologically corrects bronchoconstriction and normalizes lung function in obese mice [23].

2.2.2. Adipocytokines

There has been particular interest in the role of adipose tissue in the development of asthma in obesity. More than 50 different adipocytokines are produced by adipose tissues, and dysregulated production or secretion of adipocytokines caused by adipocyte dysfunction (*e.g.* excess adiposity) leads to the development of obesity-linked complications. Leptin is a pro-inflammatory adipocytokine, and is expressed in both lung and adipocytes. In obese individuals, serum leptin concentrations are markedly increased due to leptin resistance and hypertrophic and hyperplastic adipocytes [24]. Some studies have shown that leptin could initiate or worsen asthma [25,26]. In contrast, Arteaga-Solis E. et al. reported that leptin favors bronchodilation by inhibiting parasympathetic signaling that acts upon the M3 muscarinic receptor expressed in airway smooth muscle cells [23].

Adiponectin is an anti-inflammatory adipokine and its receptors are expressed in the lung. Adiponectin induces the expression of anti-inflammatory cytokines including IL-10, and inhibits the effects of pro-inflammatory cytokines including IL-6 and TNF-α. Airway epithelial cells express the adiponectin receptor AdipoR1 and adiponectin reduces the activation of inflammatory pathways, and increases the production of the anti-inflammatory cytokine IL-10 in a bronchial epithelial cell line [27]. Clinical studies also reported that serum adiponectin levels are decreased in asthmatic patients compared to controls [28]. However, it remains unclear whether serum adiponectin levels are altered in obese asthmatic patients [29].

3. Free fatty acids and their specific receptors

3.1. Free fatty acids

Free fatty acids are not only essential nutrients but they also exert various physiological and pathophysiological functions through free fatty acid receptors. Fatty acids are classified based on the length of their carbon chains and are grouped into long-chain fatty acids (C12-C22), medium-chain fatty acids (C7-C12), and short-chain fatty acids (C2-C6). The medium- and long-chain free fatty acids are derived through *de novo* synthesis or fat intake. Long-chain free fatty acids are important in the pathogenesis of several metabolic diseases including obesity, type II diabetes, and atherosclerosis [30]. Plasma long-chain free fatty acid concentrations are increased in obesity because the increased amount of adipose tissue mass releases more free fatty acids.

In contrast, the short-chain fatty acids are synthesized by the actions of gut microbiota (especially *bifidobacterium* and *lactobacillus*) through the fermentation of undigested carbohydrates and dietary fibers in the gastrointestinal tract. The short-chain fatty acids (SCFAs) produced in the gut are mainly acetate (C2), butyrate (C3) and propionate (C4), and are distributed systemically through the blood after colonic absorption. Short-chain fatty acids can regulate several organ functions through the activation of specific short-chain free fatty acid receptors.

3.2. Free fatty acid receptors

GPCRs are seven-transmembrane (7 TM) receptors that mediate cellular response to many diverse neurotransmitters and hormones. The family of G proteins can be divided into four subfamilies (G_q, G_i, G_s, $G_{12/13}$). In the past decade, FFAR1 (GPR40), FFAR2 (GPR43), FFAR3 (GPR41), FFAR4 (GPR120), and GPR84 have been identified as the specific receptors for free fatty acids [31–35] (Table 1). Long-chain free fatty acids act as endogenous ligands for FFAR1 and FFAR4 which couple to both G_q and G_i proteins [36–39]. Various medium- and long-chain fatty acids can activate FFAR1 at micromolar concentrations. The functional expression of FFAR1 is well documented in pancreatic β cells, where it potentiates insulin secretion [31,32]. FFAR1 is also expressed on breast cancer cell lines [36,40] and the central nervous system [41]. Activation of FFAR1 increases intracellular calcium concentrations ($[Ca^{2+}]_i$) through the activation of phospholipase C (PLC) [32], and phosphorylates proteins within the extracellular signal-regulated kinases (ERK) signaling cascade [42]. FFAR4 is expressed in adipocytes, intestine, macrophages, and the central nervous system. Activation of FFAR4 in intestine increases the secretion of glucagon-like peptide-1 (GLP-1) [35]. FFAR4 is activated by various *n*-3 or *n*-6 polyunsaturated fatty acids, including α-linolenic acid, docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) at micromolar concentrations [43]. GPR84 is a sensor for medium-chain free fatty acids and is expressed in immune-related tissues including spleen, thymus, and leukocytes [34,44].

FFAR2 and FFAR3 are both activated by short-chain fatty acids such as acetate (C2), propionate (C3), and butyrate (C4). FFAR2 couples to both G_q and G_i proteins while FFAR3 solely couples to G_i. Ligand affinity for FFAR3 is propionate > butyrate > acetate, whereas FFAR2 prefers propionate and acetate to the other short-chain FFAs.

Table 1
Characteristics of free fatty acid receptors.

Receptor	G protein coupling	Natural ligand	Synthetic ligand	Expression	Physiological function
FFAR1 (GPR40)	G_q, G_i	Long-chain FFAs Medium-chain FFAs	GW9508 TAK875 MEDICA16	Pancreatic β cell Taste bud Airway smooth muscle	Insulin secretion Regulation of taste preference Airway smooth muscle contraction Airway smooth muscle cell proliferation
FFAR2 (GPR43)	G_q, G_i	Short-cain FFAs	–	Adipose tissue Gastrointestinal tract	GLP-1 secretion Energy homeostasis
FFAR3 (GPR41)	G_i	Short-chain FFAs	–	Adipose tissue Sympathetic nervous system Vascular smooth muscle Airway smooth muscle	Energy homeostasis Pancreatic peptide YY secretion Regulate blood pressure Airway smooth muscle contraction
FFAR4 (GPR120)	G_q, G_i	Long-chain FFAs	TUG-891	Adipocytes Intestine Macrophage Central nervous sytem	GLP-1 secretion Airway smooth muscle cell proliferation
GPR84	G_i	Medium-chain FFAs	Diinodolymethane	Thymus Spleen Leukocyte	Immunostimulation Proinflammatory effects Inhibit osteoclastogenesis

FFAR2 is expressed on adipose tissue and in the gastrointestinal tract, while FFAR3 is expressed in adipose tissue, the sympathetic nervous system, and vascular smooth muscle. Recent data from *ex vivo* and *in vivo* studies have suggested that activation of FFAR3 expressed on vascular smooth muscle cells causes vasodilation and decreases systemic blood pressure [45,46]. In airways, messenger RNA of FFAR2 and FFAR3 was detected on human airway smooth muscle (HASM) cells [47,48] and human airway epithelial cells [49].

4. Roles of free fatty acid receptors in asthma

4.1. FFAR1-mediated airway smooth muscle contraction

Epidemiologic studies suggested that populations with higher *n*-6 long-chain fatty acid (such as linoleic acid) consumption have a greater asthma prevalence [50]. In the airways, mRNA encoding long-chain free fatty acid receptor FFAR1 has been demonstrated in human lung [32] and human bronchial epithelial cells [51], and we have identified protein expression of FFAR1 on the airway smooth muscle itself [52]. Activation of FFAR1 by physiological serum concentrations (5–20 μM) of the long-chain free fatty acids (oleic acid and linoleic acid) or the synthetic agonist of FFAR1 (GW9508) increased $[Ca^{2+}]_i$ in HASM cells [52]. Furthermore, long-chain free fatty acids and GW9508 induced actin reorganization (a component of airway smooth muscle cell contraction) in HASM cells. *Ex vivo* studies in guinea pig also determined that oleic acid potentiated acetylcholine-induced airway smooth muscle contraction, and attenuated the relaxant effect of the β-adrenergic agonist isoproterenol after an acetylcholine-induced airway contraction through the classical G_q-PLC/IP_3 pathway. [52]. Thus, FFAR1 expressed on airway smooth muscle contributes to airway smooth muscle contraction which could worsen asthma symptoms (Fig. 1).

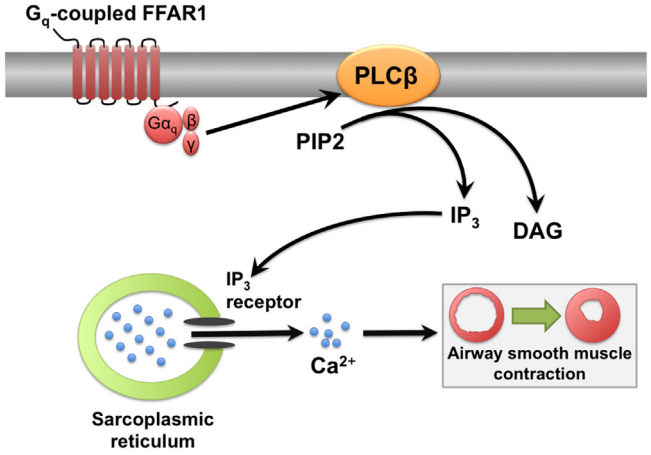

Fig. 1. FFAR1-mediated human airway smooth muscle (HASM) contraction. Gβγ subunit dissociated from FFAR1 activates phospholipase C (PLC)-β, which hydrolyzes phosphatidylinositol 4,5-bisphosphonate (PIP_2) into diacylglycerol (DAG) and inositol triphosphate (IP_3). IP_3 binds to the IP_3 receptor located on sarcoplasmic reticulum. Activation of IP_3 receptors results in Ca^{2+} efflux into the cytosol, which induces airway smooth muscle contraction.

4.2. FFAR1-mediated airway smooth muscle cell proliferation

Airway remodeling is characterized by structural changes of the airway wall such as increased airway smooth muscle mass that is induced by airway smooth muscle cell hypertrophy (increase in the size of cells) and hyperplasia (increase in the number of cells) [53,54]. Airway remodeling contributes to the progression of airway hyperresponsiveness and the severity of asthma [55]. We have identified that long-chain free fatty acids at physiological relevant concentrations (5–20 μM) induce HASM cell proliferation through MEK/ERK and PI3K/Akt signaling pathways [56]. This MEK/ERK signaling is activated by G_i-coupled FFAR1, which decreases cAMP/PKA activity perhaps through inhibition of adenylyl cyclase activity. When cAMP/PKA activity is reduced, the spontaneous inhibitory effect of PKA on c-Raf is relieved, subsequently resulting in the phosphorylation of ERK (G_i/adenylyl cyclase/cAMP/PKA/c-Raf/ERK pathway; blue arrows in Fig. 2). In addition, both the $G\alpha_q$ and Gβγ subunits which are liberated from G_i- and G_q-coupled FFAR1 contribute to ERK phosphorylation (green and red arrows in Fig. 2). G_i-coupled FFAR1 also activates the PI3K/Akt signaling which involves ras and Src (black arrows in Fig. 2). Both MEK/ERK and PI3K/Akt pathways independently induce FFAR1-mediated HASM cell proliferation (*i.e.* hyperplasia) [56]. Furthermore, the ERK signaling pathway converges on mTORC1, which is the upstream molecule of p70S6K (Fig. 2). Taken together, FFAR1 expressed on airway smooth muscle could be one of the most important regulators of airway remodeling especially in obese individuals.

4.3. Roles of FFAR4 in asthma

n-3 long-chain fatty acids such as DHA and EPA are found in fish oil, and exert anti-inflammatory effects in allergic diseases including asthma. Epidemiological and observational studies have suggested a causal relationship between decreased intake of fish oil in modernized diets and an increasing number of asthmatic patients [57]. It is also suggested that the intake of *n*-3 long-chain

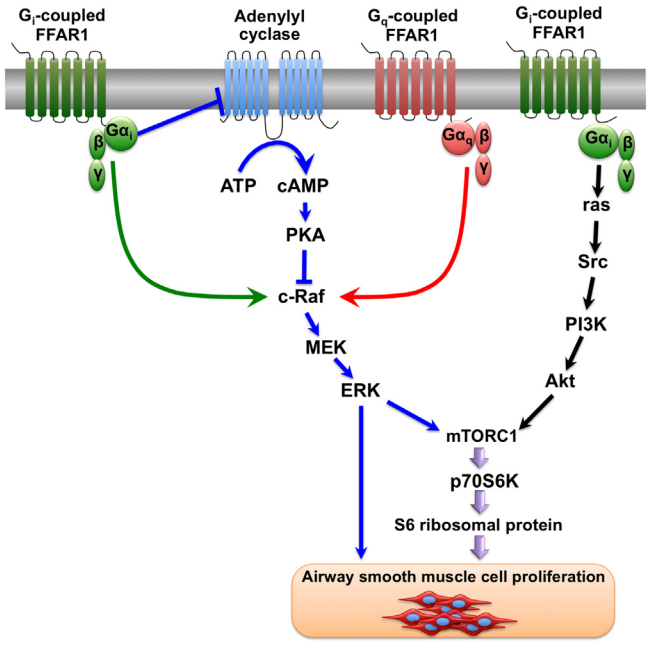

Fig. 2. Intracellular signaling pathways of FFAR1-mediated HASM cell proliferation. Blue arrows: intracellular MEK/ERK signaling pathways from G_i-coupled FFAR1 to mTORC1. Green arrows: other intracellular pathways from G_i-coupled FFAR1 to c-Raf. Red arrows: intracellular signaling pathways from G_q-coupled FFAR1 to c-Raf. Black arrows: intracellular PI3K/Akt signaling pathways from G_i-coupled FFAR1 to mTORC1. Both MEK/ERK and PI3K/Akt pathways independently induce FFAR1-mediated HASM cell proliferation. In addition, the ERK signaling pathway converges on mTORC1. Activation of mTORC1 induces phosphorylation of p70S6K, which leads to HASM cell proliferation.

fatty acids reduced asthma incidence and the prevalence of asthma symptoms [57].

Specialized pro-resolving mediators (SPM) which include resolvins, protectins, and maresins are produced by the metabolism of *n*-3 long-chain fatty acids, and inhibit airway eosinophilic inflammation and mucus production, and promote the resolution of airway inflammation [58]. The biosynthesis of the pro-resolving mediator protectin D_1 is impaired in patients with severe asthma [59].

We have determined that FFAR4, which is a sensor of *n*-3 long-chain fatty acids, is expressed on the airway smooth muscle itself [52]. However, the selective FFAR4 agonist TUG-891 did not induce actin reorganization in HASM cells, and acetylcholine-induced guinea pig airway contraction was also not affected by TUG-891. Furthermore, TUG-891 did not induce HASM cell proliferation (unpublished data). These observations suggest that FFAR4 does not contribute to the modulation of airway smooth muscle tone [52] and airway smooth muscle cell proliferation. In contrast, *n*-3 long-chain fatty acids such as EPA potentiate HASM cell proliferation, which was inhibited by the downregulation of FFAR1 in HASM cells by siRNA (unpublished data). Collectively, although *n*-3 long-chain free fatty acids and their bioactive metabolites have anti-inflammatory effects on asthmatics, *n*-3 long-chain fatty acids could contribute to airway remodeling through FFAR1 expressed on airway smooth muscle, which could worsen chronic asthma symptoms.

4.4. Roles of FFAR2 and FFAR3 in asthma

Epidemiological studies have suggested that the microbial diversity of the gut flora is important for preventing asthma (so-called "hygiene hypothesis") [60,61]. Gut microbiota regulate several organ systems by signaling through metabolic byproducts short-chain fatty acids, which are distributed systemically after colonic absorption. Short-chain free fatty acid receptors FFAR2 and FFAR3 are considered to be involved in several chronic inflammatory diseases such as obesity, asthma, and colitis. For example, FFAR2 protects against diet-induced obesity in mice [62]. However, it is controversial whether FFAR2 and/or FFAR3 have therapeutic effects on asthma. Trompette et al. [63] reported that the short-chain fatty acid propionate elicits a protective effect against allergic airway inflammation through FFAR3 but not FFAR2, while Maslowski et al. [64] reported that FFAR2-knockout mice showed an exacerbation of asthma. Mirkovic et al. [49] demonstrated that FFAR3 expressed on human bronchial epithelial cells could induce excessive IL-8 production. Further studies are required to elucidate the potential roles of short-chain fatty acid receptors in asthma.

5. Conclusion

The impact of obesity on the development, severity, and prognosis of asthma is an area of growing research interest with a goal of increasing our understanding of the close association between adipose tissue and respiratory systems. Our findings suggest that the long-chain free fatty acids and their specific receptors FFAR1 expressed on airway smooth muscle could be an important modulator of airway smooth muscle tone and its remodeling, and may play a pivotal role linking obesity to asthma. Further studies are needed to elucidate the relationship between the obesity-induced asthma and dysregulation of free fatty acid metabolism, which could increase serum free fatty acid concentration.

Conflicts of interest

The authors declare that they have no competing interests.

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