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PPARs: Key Regulators of Airway Inflammation and Potential Therapeutic Targets in Asthma

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Abstract

Asthma affects approximately 300 million people worldwide, significantly impacting quality of life and healthcare costs. While current therapies are effective in controlling many patients' symptoms, a large number continue to experience exacerbations or treatment-related adverse effects. Alternative therapies are thus urgently needed. Accumulating evidence has shown that the peroxisome proliferator-activated receptor (PPAR) family of nuclear hormone receptors, comprising PPARα, PPARβ/δ, and PPARγ, is involved in asthma pathogenesis and that ligand-induced activation of these receptors suppresses asthma pathology. PPAR agonists exert their anti-inflammatory effects primarily by suppressing pro-inflammatory mediators and antagonizing the pro-inflammatory functions of various cell types relevant to asthma pathophysiology. Experimental findings strongly support the potential clinical benefits of PPAR agonists in the treatment of asthma. We review current literature, highlighting PPARs' key role in asthma pathogenesis and their agonists' therapeutic potential. With additional research and rigorous clinical studies, PPARs may become attractive therapeutic targets in this disease.

Keywords

PPAR; rosiglitazone; allergy; mucus; pulmonary

1. Introduction

Asthma affects people of all ages worldwide, although its prevalence can vary widely depending on the specific demographics examined [1, 2]. An estimated 300 million individuals are affected by the disease, but its impact goes far beyond the patients themselves, involving families and communities and presenting a significant socioeconomic burden [1]. Clinically, asthma encompasses a heterogeneous group of phenotypes characterized by wheezing, coughing, dyspnea, chest tightness, and reduced expiratory

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airflow [2]. Pathologically, asthma is characterized by airway inflammation, remodeling, and hyperresponsiveness [3]. Underlying these anatomical and functional aberrations is the development of an abnormal T helper 2 (Th2) immune response [4, 5]. This response features an upsurge of Th2 lymphocytes that elevates production of interleukin-4 (IL-4), a cytokine promoting immunoglobulin E (IgE) synthesis, as well as of IL-5, which recruits eosinophils. Several other cell types and mediators are also involved in asthma pathogenesis. Airway epithelial cells, for instance, normally protect the lungs by serving as the first line of defense but, when impaired or dysregulated, contribute to inflammation, remodeling, and mucus hypersecretion by producing vasoactive factors, pro-inflammatory agents, growth factors, and metalloproteinases. When the epithelium is compromised under pathological conditions, the interstitial tissue is also altered due to fibroblast proliferation and differentiation, collagen deposition, and hypertrophy and hyperplasia of airway smooth muscle cells that also produce pro-inflammatory factors [4, 5]. Another key player in asthma pathogenesis is the alveolar macrophage. As initial responders to external insults, these leukocytes, along with the airway epithelium, provide host defenses [4, 6] via their phagocytic function and secretion of appropriate molecules [7, 8]. Notably, to minimize subsequent tissue injury as well as to maintain healthy lung physiology and gas exchange, their regulation of immune responses is normally tightly controlled [4, 6, 9]. When dysregulation of their activities results in an imbalance between their anti- and pro-inflammatory responses [6, 8, 10], however, lung homeostasis is disrupted, as is seen in asthma. In fact, alterations of alveolar macrophage function have been observed in patients [4, 6].

Current standard therapies, most notably corticosteroids and β2-adrenergic receptor agonists, effectively control symptoms and enhance lung function in many patients [11]. However, some individuals experience adverse events from these treatments while others face acute exacerbations without adequate improvement [5, 12]. These shortcomings of conventional treatments, combined with asthma's global burden, heighten the need for development of alternative, more effective therapies.

Peroxisome proliferator-activated receptors (PPARs), comprising PPARα, PPARβ/δ, and PPARγ, are nuclear hormone receptors initially recognized for their functions in lipid regulation and glucose metabolism [13]. As ligand-activated transcription factors ubiquitously expressed throughout the body [4, 14, 15], they are now known to also play a role in cellular processes such as differentiation, proliferation, survival, apoptosis, and motility in a variety of biological contexts including inflammation and immune responses [5, 16]. Cells of the immune system that infiltrate the airways following inflammatory stimuli (*e.g.* dendritic cells, eosinophils, macrophages, mast cells, monocytes, and neutrophils, as well as B and T lymphocytes) have been found to express PPARs [5]. Importantly, PPAR expression is altered during inflammatory responses, including airway inflammation, suggesting PPARs' involvement in asthma pathogenesis [4, 5]. Retrospective studies examining Chinese children [17] and adults [18] have provided further evidence by reporting correlations between certain PPAR single nucleotide polymorphisms and asthma risk and prognosis [17, 18]. These findings also highlight PPARs' potential as a predictive and prognostic molecular marker.

A variety of naturally occurring molecules and synthetic compounds activate PPARs. PPARα agonists include polyunsaturated and saturated fatty acids and eicosanoids (*e.g.* 8(*S*)-hydroxyeicosatetraenoic acid and leukotriene B_4) as well as synthetic fibric acid derivatives (*e.g.* bezafibrate, clofibrate, and fenofibrate) and pirinixic acid (WY-14643) [5, 13, 16, 19]. Polyunsaturated and saturated fatty acids such as prostacyclin and other eicosanoids (*e.g.* prostaglandin A_1 and prostaglandin D_2) activate PPARβ/δ [5, 16]. Synthetic, high-affinity agonists for PPARβ/δ include GW501516, L165041, GW0742, and L783483 [4, 5, 20]. PPARγ is stimulated by saturated and polyunsaturated fatty acids, eicosanoid derivatives such as 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2), and nitrated fatty acids [13, 14, 21, 22]. Thiazolidinediones (TZDs) such as pioglitazone, rosiglitazone, troglitazone, and ciglitazone are the most notable synthetic PPARγ agonists [13].

Although studies have provided evidence for ligand-independent transcriptional activity, ligand-dependent functions of PPARs are better known and more widely accepted [23]. In this latter, conventional model, PPARs in their basal state are bound by corepressors that restrain their transcriptional activity [24]. PPAR agonists, however, trigger a conformational change that dissociates corepressors and favors coactivator interaction [25, 26]. The presence of coactivators accompanied by chromatin remodeling allows the receptors to heterodimerize with retinoid X receptors and bind to specific PPAR response elements (PPREs) in the promoters of their target genes, thus activating these genes' transcription [24–26]. Ligand binding also promotes ubiquitin-proteasome system-mediated degradation of corepressors [25].

In addition to corepressor/coactivator switches, post-translational modifications also regulate PPAR expression and activity. One such modification is phosphorylation, which can modulate PPARs' affinity for ligands, cofactors, retinoid X receptors, and target genes [23]. Depending on the cellular contexts and signals at play, phosphorylation can be stimulatory or suppressive [24]. Another post-translational modification is SUMOylation, which inhibits PPAR activity by promoting corepressor binding [24]. A third such modification is ubiquitination; ubiquitinated PPARs are subject to proteasomal degradation, thus downregulating their expression and activity [24].

Accumulating experimental evidence, with the majority focusing on PPARα or PPARγ, has shown that all three PPARs modulate the intensity, duration, and outcomes of inflammatory responses and that PPAR activation is anti-inflammatory and beneficial in various diseases associated with inflammation [4, 16, 27]. The cellular targets of this anti-inflammatory PPAR function are not only inflammatory cells of the immune system but also resident and structural cells of the airways that play significant roles during inflammation [4, 14].

At the molecular level, multiple mechanisms account for PPARs' anti-inflammatory effects. One such mechanism is coactivator sequestration: by competing for coactivators, PPARs limit the ability of pro-inflammatory transcription factors to access these required cofactors and initiate transcription of their target pro-inflammatory genes [13, 14]. PPARs can also inhibit inflammatory gene expression by stabilizing corepressor binding [24]. In addition, PPARs can directly bind to pro-inflammatory transcription factors, interfering with their access to coactivators or promoting corepressor recruitment, and consequently suppress their downstream gene transcription [24]. Transcription factors regulated this way by PPARs are major mediators of inflammatory responses and include activator protein-1 (AP-1), CCAAT/enhancer binding protein (C/EBP), nuclear factor of activated T cells (NFAT), nuclear factor-κB (NF-κB), and signal transducers and activators of transcription (STAT) [4]. Lastly, PPAR agonists have been shown to modulate c-Jun N-terminal kinase (JNK) and mitogen-activated protein kinase (MAPK) activities, indirectly suppressing inflammatory responses [24]. Besides these mechanisms, PPARs regulate expression of inflammatory modulators by binding to PPREs found in their promoters [28–30]. Thus, acting through pathways distinct from those employed by traditional therapies, PPAR-targeted asthma therapy could potentially prevent disease complications, progression, and exacerbations.

2. Roles of PPARs in Asthma

2.1 Overview

In general, expression and activity of each PPAR subtype is associated with protection against asthma or reduction in its severity, whereas impairment of a PPAR's function or expression leads to or exacerbates the disease. These effects target both inflammation and tissue remodeling, two prominent features of asthma. All three PPAR subtypes counteract inflammatory responses by modulating pro- and anti-inflammatory mediators as well as by reducing the expression of adhesion and chemotactic molecules essential for leukocyte recruitment. The specific molecules affected are not fully identical across the three subtypes, however.

PPARs also contribute to the preservation of tissue integrity in multiple ways. PPARα and PPARγ downregulate matrix metalloproteinases involved in extracellular matrix degradation, an essential aspect of tissue degradation and remodeling. PPARβ/δ and PPARγ suppress lung fibroblasts' proliferation and their differentiation into myofibroblasts, further blocking increased collagen deposition. PPARγ also inhibits epithelial and smooth muscle hyperplasia as well as blocking mucus overproduction. In the following sections, these multifaceted anti-asthma functions of each PPAR subtype are discussed in more detail.

2.2 PPARα

PPARα was first shown to control the duration of inflammatory responses in a mouse ear-swelling model [31]. *In vitro* and *in vivo* studies have since identified a variety of mechanisms by which PPARα exerts its anti-inflammatory effect, including antagonism of inflammatory cell functions. For example, WY-14643 promotes apoptosis of human monocyte-derived macrophages [32]. PPARα activation also reduces production of multiple pro-inflammatory mediators, including tumor necrosis factor-α (TNF-α), IL-1α, IL-6, and IL-8, in multiple skin inflammation models [33, 34]. It also reduces production of TNF-α and IL-6 by monocytes *in vitro* [35], and of IL-6 and IL-8 by aortic smooth muscle cells in atherosclerosis models [36, 37]. In chronic inflammatory conditions, such as those characterized by constitutive NF-κB activation and elevated levels of pro-inflammatory cytokines, WY-14643 treatment similarly suppresses TNF-α and IL-6 production [38]. Conversely, PPARα deficiency exacerbates inflammatory features such as IL-6 and IL-12 production [39]. Furthermore, Ye *et al.* found that fenofibrate treatment reduced TNF-α and

IL-6 levels in individuals with hypertriglyceridemia, a condition often associated with increased inflammatory markers [40].

In addition to suppressing pro-inflammatory cytokines, PPARα activation controls expression or production of adhesion and chemotactic molecules that are imperative to inflammatory responses. Highlighting the essential role of PPARα in migration, adhesion, and recruitment of immune cells, Michalik *et al.* showed that skin wound healing, where such migration is beneficial, was impaired in PPARα-deficient mice [41]. Conversely, WY-14643 hinders pro-inflammatory neutrophil infiltration by suppressing intercellular adhesion molecule-1 (ICAM-1) expression in gingivomucosal tissues of rats with periodontitis [42], as well as in inflamed colons of mice with inflammatory bowel disease [43]. In the latter study, PPARα knockout mice showed signs of more severe colonic injury than did wild-type animals. Vascular cell adhesion molecule-1 (VCAM-1) expression in human aortic endothelial cells [44] and human carotid artery endothelial cells [45] is similarly reduced by WY-14643 and fenofibrate in *in vitro* inflammation models, consequently suppressing monocyte/macrophage binding to such cells. WY-14643 and fenofibrate treatments likewise reduce monocyte chemoattractant protein-1 (MCP-1) secretion from human umbilical vein endothelial cells [46].

Matrix metalloproteinases (MMPs), particularly MMP-9, contribute to inflammation by promoting extracellular matrix degradation during tissue remodeling associated with chronic inflammation and also by assisting infiltration of inflammatory cells through the basement membrane [4]. WY-14643 reduces MMP-9 expression in rat mesangial cells [47], while fenofibrate similarly decreases MMP-9 secretion by human monocytic cells [48].

In addition to inhibiting expression and activity of pro-inflammatory agents, activated PPARα can induce anti-inflammatory agents. For example, fenofibrate increases IL-10 expression during experimental autoimmune myocarditis in mice [49] and WY-14643 promotes expression of anti-inflammatory sIL-1 receptor antagonist (sIL-1ra) [50]. Furthermore, WY-14643, fibrates, and another PPARα agonist, GW9578, are known to induce IκBα expression, thereby hindering NF-κB's pro-inflammatory activity [51, 52]. Together these studies demonstrate that PPARα controls inflammatory responses not only via downregulation of pro-inflammatory molecules but also via upregulation of anti-inflammatory mediators.

Consistent with the above findings in other organs and disease models, current data support the anti-inflammatory effect of PPARα activation in the lungs and the airways. In murine models of allergic airway disease, PPARα deficiency exacerbates asthmatic features such as airway hyperresponsiveness and eosinophilia, while treatment with PPARα agonists shows the opposite trend [53–55]. In an experimental model of pleurisy, clofibrate treatment adds to the anti-inflammatory activity of the synthetic glucocorticoid dexamethasone [56]; combination therapy significantly downregulates macrophage and other inflammatory cell infiltration into the pleural cavity and thereby reduces tissue injury. Conversely, the absence of PPARα compromises dexamethasone's control of lung inflammation in mice [56]. Thus, PPARα agonists not only have the potential to be useful as monotherapy but also may function synergistically with glucocorticoids in asthma treatment. Together, these studies support the anti-inflammatory effects of PPARα activation and justify further investigation of the receptor's role in asthma and airway inflammation.

2.3 PPARβ/δ

Studies using high-affinity ligands such as GW501516 and GW0742 have shown that PPARβ/δ modulates many mediators of inflammation [57–60]. In monocytes/macrophages, this anti-inflammatory function of PPARβ/δ rests in part on ligand binding-induced dissociation from the transcriptional repressor B cell lymphoma-6 (Bcl-6) protein; this uncoupling releases Bcl-6 to suppress expression of pro-inflammatory molecules [57, 60]. More directly, PPARβ/δ activation by GW501516 antagonizes inflammation by inducing expression of sIL-1ra [61] and transforming growth factor-β1 (TGF-β1) [62]. Like PPARα- and PPARγ-activating ligands, PPARβ/δ agonists suppress endothelial cells' expression of adhesion molecules such as VCAM-1, ICAM-1, and E-selectin that are required for leukocyte recruitment [63–66] as well as the chemokines MCP-1 and growth-regulated oncogene-α (GROα) [63, 65, 66].

PPARβ/δ is also involved in wound healing-relevant functions of keratinocytes, which express PPARβ/δ more abundantly than the other PPAR isotypes [67]. PPARβ/δ upregulates anti-apoptotic genes and downregulates pro-apoptotic genes, resulting in keratinocyte survival [68]. The activated receptor further enhances wound healing both by potentiating keratinocytes' migratory response to injury via enhancement of chemotactic signals and by promoting integrin recycling and actin cytoskeleton remodeling [69]. An *in vivo* study has validated this conclusion by showing that PPARβ/δ-deficient mice exhibit an impaired wound-healing response [41].

A PPARβ/δ ligand was initially shown ineffective in controlling allergen-induced airway inflammation in mice [55]. However, a later study demonstrated that GW0742 inhibits lipopolysaccharide-induced neutrophil infiltration into lung tissues and hinders production of IL-6, IL-1β, and TNFα, thus diminishing the extent of inflammatory responses [70]. Furthermore, GW0742 blocks pulmonary fibroblast proliferation [71] and controls leukocyte infiltration and tissue damage in a mouse model of pulmonary fibrosis [72]; subepithelial fibrosis is a prominent component of airway remodeling during asthma pathogenesis. Of note, the discrepancy in findings between Trifilieff *et al.* and Haskova *et al.* may result from differences in the timing of PPARβ/δ agonist administration. Alternatively, the observed disagreement may reflect use of different disease models. In summary, although accumulating evidence supports the anti-inflammatory properties of PPARβ/δ agonists, additional studies are needed to elucidate the role of PPARβ/δ in airway inflammation and to assess its prospect as a therapeutic target for asthma.

2.4 PPARγ

PPARγ's expression by various cells of the immune system underscores its prominent role in inflammatory responses [14, 16, 73, 74]. Following initial recognition as a regulator of monocytes/macrophage function in atherosclerosis [73], PPARγ is now known to regulate functions of other inflammation-associated cell types [4, 13, 74, 75] in various disease and disease model contexts [4, 73, 75]. Furthermore, many inflammatory conditions are associated with alterations in PPARγ expression and activity, and such changes are believed to contribute significantly to several diseases [5, 76]. As its involvement in inflammation has been extensively reviewed elsewhere [14, 16, 73], the focus in this review will be placed on PPARγ's role in asthma.

IL-4, a cytokine that promotes the Th2 responses associated with asthma pathogenesis, induces PPARγ in airway epithelial cells [77]. To substantiate this *in vitro* finding, studies using a murine model of allergic airway disease observed higher levels of PPARγ in the lung tissues of animals exposed to the allergen ovalbumin (OVA) [78–80]. This upregulation of PPARγ was localized to airway epithelial cells, smooth muscle cells, mast cells, and some inflammatory cells [80]. The link between asthma pathogenesis and PPARγ expression levels is emphasized by a study showing that asthmatic patients exhibit greater PPARγ expression in their bronchial submucosa, bronchial epithelium, and airway smooth muscle than do healthy controls, and that this upregulation is reversed by glucocorticoid treatment [81]. It has been speculated that increased PPARγ expression is a cellular response to pro-inflammatory cytokines that initiates a negative feedback pathway limiting airway inflammation [5]. In contrast, alveolar macrophages of allergen-challenged asthmatic patients were shown to have reduced PPARγ levels compared to those in controls [82]. The authors suggest that this downregulation could potentially contribute to airway inflammation. Alternatively, the findings by Honda *et al.* showing that the increase in PPARγ expression in allergen-sensitized and –challenged animals was blocked by ciglitazone treatment [80] offer another plausible explanation: this PPARγ downregulation from otherwise elevated levels may be a consequence of PPARγ activation-induced reduction or resolution of airway inflammation [4, 5]. Thus, while PPARγ levels appear to influence asthma pathogenesis, analysis and interpretation of expression data must include careful consideration of the complex interaction between PPARγ and the stage of inflammation (*i.e.* initiation vs. resolution) [5].

PPARγ activation/PPARγ agonists have displayed beneficial effects on multiple asthma features. For example, in a mouse model of OVA-induced allergic airway disease, rosiglitazone reduced airway hyperresponsiveness [83]. In another mouse model, which induces allergic airway disease via cockroach allergen, pioglitazone demonstrated the same effect as well as suppression of leukocyte infiltration, pro-inflammatory chemokine and cytokine production, and mucus overproduction [84]. Importantly, effects on pathophysiological responses and cytokine and chemokine production were comparable between pioglitazone and dexamethasone. Furthermore, ciglitazone significantly suppresses airway inflammation and remodeling in addition to airway hyperresponsiveness, eosinophilia, mucus overproduction, cytokine production, and collagen deposition [53, 80, 85]. Yet another PPARγ agonist, troglitazone, inhibits IL-5-mediated survival and eotaxin-directed chemotaxis of eosinophils [86], indicating its efficacy against eosinophilia. Significantly, Mueller *et al.* reported that ciglitazone administered later in the course of allergen exposure is also effective in reducing airway inflammation, as suggested by decrease in inflammatory cell infiltration and epithelial hyperplasia in the lungs [85].

PPARγ agonists suppress functions of inflammatory cells other than eosinophils. Rosiglitazone decreases lymph node infiltration of lung dendritic cells, critical inducers of immune responses, in OVA-treated animals [87, 88], and thus reduces airway inflammation [88]. OVA-induced inflammation assessed by bronchoalveolar lavage is also reduced by the synthetic PPARγ agonist GI262570 [55]. In addition to suppressing pro-inflammatory cytokine production, 15d-PGJ_2 and troglitazone enhanced phagocytosis of apoptotic neutrophils by human alveolar macrophages, an important aspect of inflammatory resolution [89]. These macrophages also show upregulated CD36 expression after PPARγ agonist treatment. Consistently, another study using a bleomycin-induced lung fibrosis model reported that enhancement of alveolar macrophages' efferocytotic ability in the presence of apoptotic cells was reversed by the PPARγ antagonist GW9662 [90], emphasizing the prominent role of PPARγ in macrophage regulation.

PPARγ activation also regulates structural cells involved in airway inflammation. An *in vitro* study showed both 15d-PGJ_2 and ciglitazone inhibited proliferation and induced apoptosis of human airway smooth muscle cells, whose hypertrophy and hyperplasia contribute significantly to asthma-associated airway narrowing [91]. In addition, rosiglitazone and pioglitazone have been shown to reduce MMP-9 activity and protein expression in TNF-α- or phorbol 12-myristate 13-acetate (PMA)-stimulated human bronchial epithelial cells [92], thus suggesting their efficacy against the tissue remodeling observed during asthma pathogenesis.

Airway smooth muscle cells also contribute to inflammation by secreting granulocyte-macrophage colony-stimulating factor (GM-CSF), a cytokine critical for survival and activity of various leukocytes, including eosinophils [91], and 15d-PGJ_2 and ciglitazone suppress GM-CSF release [91]. This finding provides further evidence for the effectiveness of PPARγ agonists against inflammation. Moreover, 15d-PGJ_2 and ciglitazone downregulate IL-8 secretion from airway epithelial cells [77], which is expected to primarily reduce neutrophil recruitment during airway inflammation. PPARγ agonists also decrease lung expression of ICAM-1 and VCAM-1 as well as levels of eotaxin and regulated upon activation normal T cell expressed and secreted (RANTES) in a mouse model of occupational asthma [93].

Lung injury, especially to the alveolar epithelium, induces fibroblasts to proliferate and differentiate into myofibroblasts that produce excessive collagen and other extracellular matrix components [4, 94–96]. 15d-PGJ_2, troglitazone, ciglitazone, and rosiglitazone [95, 96] as well as constitutively active PPARγ [95] prevent human lung fibroblasts from differentiating into myofibroblasts [95, 96]. PPARγ agonists also suppress collagen secretion from these cells [95, 96] and inhibit bleomycin-induced pulmonary fibrosis [95]. Taken together, the studies cited in this section provide evidence for multifaceted anti-inflammatory effects of PPARγ in the lungs and suggest that its agonists may become useful in asthma intervention.

3. Therapeutic Implication of PPAR Ligands for Asthma

Collectively, experimental findings strongly support the clinical benefits of PPAR agonists as asthma treatments. Unfortunately, however, clinical data are currently available only for PPARγ agonists. Supporting the value of PPARγ agonists as asthma therapy, a recent retrospective cohort study analyzing a large number of diabetic patients with asthma found an association between TZD use (for diabetes treatment) and reduction in the risk of asthma exacerbations as well as in oral steroid prescriptions [97]. Another study of 16 steroid-naïve asthmatic patients also reported that 12 weeks of rosiglitazone treatment improved airway hyperresponsiveness (assessed by response to methacholine) [98]. In agreement with these clinical studies, a case report described improvement of asthma with pioglitazone treatment [99]: a 71-year-old man with type 2 diabetes, hyperlipidemia, hypertension, and asthma experienced disappearance of wheezing after several days of pioglitazone treatment. Another diabetic man with asthma also showed similar clinical improvement [99]. Moreover, upon discontinuation of pioglitazone, his respiratory symptoms returned, emphasizing the association between pioglitazone treatment and recovery from asthma.

Still, the efficacy of PPARγ agonists as asthma drugs remains controversial. A randomized study of 46 asthmatic patients failed to observe improvement in asthma symptoms (assessed by Asthma Control Questionnaire score) after 4-week rosiglitazone treatment, although it did find that the treatment enhanced patients' lung function [100]. Likewise, in a placebo-controlled, randomized study of 32 asthma patients, 4-week rosiglitazone treatment only modestly decreased late phase asthma reactivity to allergen challenge, leading the authors to conclude that rosiglitazone would not provide adequate intervention [101]. A double-blind, randomized controlled trial of 68 asthma patients reached a similar conclusion after observing no sign of improvement after 12 weeks of pioglitazone [102]. It is noteworthy, however, that all these studies are associated with some limitations such as a small sample size and non-general subjects. Thus, larger randomized, placebo-controlled studies should be conducted with various types of asthma patients to substantiate the clinical effects of PPARγ agonists. Similar studies on the use of PPARα and PPARβ/δ agonists can be expected to provide further insights into asthma treatment.

4. Conclusions

Traditional asthma therapies, although effective for many patients, provide only temporary symptomatic alleviation [103]. Moreover, even with these interventions, some patients still experience exacerbations and progressive deterioration of pulmonary function [5, 12]. Understanding the fundamental pathophysiology is thus critical for advances in asthma therapy. Accumulating experimental findings support all three PPARs' anti-inflammatory properties and involvement in airway inflammation. Clinical data available for PPARγ agonists also substantiate their therapeutic potential. Unfortunately, PPARγ agonists are associated with side effects: rosiglitazone and pioglitazone have been shown to cause weight gain, edema, and congestive heart failure [104] as well as bone fractures [105]; troglitazone is associated with hepatotoxicity and has therefore been withdrawn from clinical use [106]. Thus, to minimize these adverse effects, the drugs may be best administered via inhalation as opposed to systemic delivery [27]. Importantly, local administration of the drugs in murine models has been shown to provide similar benefits to those seen with systemic delivery on multiple pathological features of asthma, including elevated cytokine production, airway hyperresponsiveness, and eosinophilia, [53, 55], thus supporting inhalational drug delivery.

Another strategy to circumvent or reduce the side effects associated with PPAR agonists or traditional therapies is to employ combinations of drugs, each at a lower concentration that may offer limited benefit as monotherapy. In fact, PPARγ agonists have demonstrated synergistic effects with corticosteroids and β2-adrenergic receptor agonists. In a mouse model of inflammation, individually ineffective doses of rosiglitazone and dexamethasone reduced paw edema when administered together [107]. The β2-adrenergic receptor agonist salbutamol also displayed synergy with 15d-PGJ_2 or rosiglitazone in reduction of human bronchial smooth muscle cell proliferation [108]. Additive inhibition of TNF-α-induced chemokine production was similarly observed with 15d-PGJ_2 and the glucocorticoid fluticasone as well as 15d-PGJ_2 and the β2-adrenergic receptor agonist salmeterol [109]. As noted, clofibrate also showed synergy with dexamethasone in a mouse pleurisy model [56]. These data suggest combination therapy may be an attractive option. Thus, with further investigation and clinical trials, PPAR agonists may become an effective part of asthma therapy.

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Abbreviations

15d-PGJ_2	15-deoxy-$\Delta^{12,14}$-prostaglandin J_2
AP-1	Activator protein-1
Bcl-6	B-cell lymphoma-6
C/EBP	CCAAT/enhancer binding protein
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GRO-α	Growth-regulated oncogene-α
ICAM-1	Intercellular adhesion molecule-1
IgE	Immunoglobulin E
IL	Interleukin
JNK	c-Jun N-terminal kinase
MAPK	mitogen-activated protein kinase
MCP-1	Monocyte chemotactic protein-1
MMP	Matrix metalloproteinase
NFAT	Nuclear factor of activated T cells
NF-κB	Nuclear factor-κB
OVA	Ovalbumin

PMA	Phorbol 12-myristate 13-acetate
PPAR	Peroxisome proliferator-activated receptor
PPRE	PPAR response element
RANTES	Regulated upon activation normal T cell expressed and secreted
sIL-1ra	Secreted IL-1 receptor antagonist
STAT	Signal transducers and activators of transcription
TGF-β1	Transforming growth factor-β1
Th2	T helper 2
TNF-α	Tumor necrosis factor-α
TZD	Thiazolidinedione
VCAM-1	Vascular cell adhesion molecule-1

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