Peroxisome proliferator-activated receptors: a therapeutic target in COPD?

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PERSPECTIVE

Peroxisome proliferator-activated receptors: a therapeutic target in COPD?

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ABSTRACT: Extrapulmonary pathology significantly impairs clinical outcome in chronic obstructive pulmonary disease (COPD).

The peroxisome proliferator-activated receptors (PPARs) are implicated in the regulation of several hallmarks of systemic COPD pathology, including cachexia, decreased oxidative muscle metabolism, oxidative stress and systemic inflammation.

Recently, expression of PPARs and related cofactors was shown to be reduced in peripheral skeletal muscle of patients with moderate-to-severe COPD and muscle weakness.

The current authors hypothesise that impaired peroxisome proliferator-activated receptor signalling may underlie some of the muscular disturbances in chronic obstructive pulmonary disease. Proposed mechanisms will be outlined in the present article, as well as the therapeutic potential of peroxisome proliferator-activated receptor modulation in the treatment of skeletal muscle dysfunction.

KEYWORDS: Chronic obstructive pulmonary disease, inflammation, oxidative stress, peroxisome proliferator-activated receptors, skeletal muscle

Chronic obstructive pulmonary disease (COPD) is a lung disease characterised by irreversible airway obstruction and an abnormal chronic inflammatory response of the airways. Dominant symptoms are dyspnoea and impaired exercise capacity. These symptoms lead to progressive disability and poor health status, but correlate poorly with severity of local impairment in the lungs. Surprisingly, even in the most recent international guidelines for diagnosis of COPD, staging is still only based on severity of airway obstruction [1]. However, there is increasing evidence in the literature that COPD should not be considered as a localised pulmonary disorder but as a systemic disease involving pathology in several extrapulmonary tissues. Well-characterised systemic features are a chronic low-grade systemic inflammation and altered protein metabolism which, in a subgroup of severe COPD patients, initially results in muscle atrophy only (commonly referred to as sarcopaenia) and in later stages also in cachexia [2, 3]. Muscle atrophy is associated with increased mortality risk independent of disease staging [4]. Besides muscle atrophy, it is well established that intrinsic abnormalities in structure and metabolism are present in the remaining muscle in moderate-to-severe COPD. Muscle atrophy and muscle dysfunction both contribute to reduced strength and endurance of the muscle, which in turn limits exercise capacity. A recent meta-analysis showed that skeletal muscle in patients with moderate-to-severe COPD shows a fibre-type shift from type I oxidative fibres to type II glycolytic fibres [5]. In addition, skeletal muscle in patients is characterised by a reduced oxidative capacity and recently *in vitro* impaired mitochondrial respiration was even shown in underweight patients with severe COPD [6].

It is still unclear whether the molecular mechanisms of muscular impairment in COPD are governed by disease-specific factors or common denominators of chronic wasting disease. The elucidation of these mechanisms is a crucial step towards developing specific therapies aimed at improving functionality and health status of these patients. Intriguingly, oxidative capacity and fibre-type composition of skeletal muscle are controlled or affected by signalling through the nuclear receptor family of peroxisome proliferator-activated receptors (PPARs) [7]. Moreover, PPARs have also been shown to possess important anti-inflammatory properties by modulation of inflammatory signalling through the nuclear factor (NF)-κB pathway [8]. These combined actions could make

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PPARs an attractive target for therapeutic intervention aimed at alleviating skeletal muscle weakness in COPD, as will be highlighted in the present article.

PPARS AND COPD

Three PPAR isoforms, α, β/δ and γ, can be distinguished. All three exhibit tissue-specific expression, ligand-specific activation and the ability to heterodimerise with retinoid X receptors, resulting in the transcription of target genes. During the past decade, PPARs have been implicated in several physiological processes, such as the regulation of lipoprotein and lipid metabolism, glucose homeostasis, the inflammatory response and cellular differentiation [9].

PPAR-α is expressed in many oxidative tissues, including skeletal muscle. The primary role of PPAR-α in skeletal muscle is regulation of fatty acid homeostasis and transcriptional control of lipid regulatory genes [10]. Additionally, PPAR-α is involved in the regulation of amino acid metabolism by downregulating blood and tissue branched-chain amino acid levels [11]. Other effects of PPAR-α activation include attenuation of inflammatory responses through inhibition of NF-κB driven gene transcription [12]. Interestingly, secretion of inflammatory mediators in the lung decreased upon PPAR-α activation in a mouse model of chronic lung inflammation [13]. PPAR-α is activated by a number of naturally occurring, lipid-derived molecules including long-chain fatty acids, eicosanoids and leukotriene B_4, while the fibrate class of hypolipidaemic drugs, including fenofibrate and gemfibrozil, serve as synthetic PPAR-α ligand.

Although most abundant in adipose tissue, PPAR-γ is expressed at low levels in skeletal muscle. Interestingly from a pulmonary perspective, PPAR-γ is also expressed in the human lung. PPAR-γ regulates the storage of fat in adipose tissue and reduces plasma glucose, lipid and insulin levels in animal models of type 2 diabetes mellitus, as well as in humans [14]. Like PPAR-α, PPAR-γ is involved in attenuation of the inflammatory response by reducing NF-κB DNA binding and repression of NF-κB activation through inhibition of the NF-κB inhibitor protein (IκB) kinase complex activity [12, 15]. Anti-inflammatory effects of PPAR-γ activation in the lung have been shown consistently in experimental models of asthma and other airway diseases, such as COPD [16]. PPAR-γ is the main target of the thiazolidinedione (TZD) class of insulin-sensitising drugs, which are currently a mainstay of therapy for type 2 diabetes mellitus. Besides these synthetic ligands, PPAR-γ is activated by several naturally occurring compounds, such as prostaglandin J2 derivates and polyunsaturated fatty acids (PUFAs) [17].

PPAR-δ is a powerful regulator of fatty acid utilisation and energy homeostasis in several tissues, including the heart and skeletal muscle [7]. Consistent with such a role, PPAR-δ protein content is increased during physiological conditions characterised by elevated fatty acid utilisation, such as physical exercise or fasting. However, as PPARs are transcriptional regulators, their functionality is not only determined by abundance, but also by their activity. This may explain apparently contradictory reports showing increased PPAR-δ expression in skeletal muscle following short-term fasting *versus* decreased PPAR-δ expression after longer periods of fasting [18, 19]. Therefore, selection of different time points, as well as PPAR abundance and activity measurements are necessary to clarify the actual sequence of events in skeletal muscle during metabolic adaptation. Overexpression of PPAR-δ or its activation by synthetic agonists strongly increases the lipid catabolic activities of skeletal muscle, not only by upregulating genes involved in this metabolic pathway, but also by inducing mitochondrial biogenesis and by promoting an increment of oxidative fibres [20]. PPAR-δ is characterised by the large size of its ligand-binding pocket, which allows interaction with a greater variety of activators when compared with other nuclear hormone receptors. PPAR-δ is activated by PUFAs, prostacyclin and synthetic molecules, such as phenoxyacetic acid derivates (*e.g.* GW 501516 and GW 0742) [17].

The current authors recently showed that PPAR-δ protein content is reduced in skeletal muscle of COPD patients compared with healthy control subjects [21]. In addition, mRNA- levels of the PPAR co-activator 1α (PGC-1α), which is a PPAR-γ co-activator and a master regulator of mitochondrial biogenesis, were lower in COPD patients compared with controls, and mRNA levels of PPAR-α were significantly lower in cachectic patients compared with noncachectic patients [21]. Muscle oxidative phenotype, which is positively influenced by PPAR-δ, PGC-1α and PPAR-α, is reduced in COPD [6]. This suggests that a reduced PPAR-δ and/or PPAR-α content or function in this disease may be involved in the observed reduction in muscular oxidative capacity that may even lead to mitochondrial dysfunction. Many pathological hallmarks of COPD have been shown to exert a negative effect on PPAR expression and activity. Hypoxia and inflammation could be responsible for lower PPAR expression levels or protein content, as there are several reports that suggest a negative influence of these parameters on PPAR levels [22–24]. Furthermore, a sedentary lifestyle, which is often adopted by COPD patients due to disease-specific limitations, can also underlie reduced levels of PPAR and PGC-1α in skeletal muscle, as it has been shown that physical activity level is an important factor regulating these factors [25, 26]. Intriguingly, in other disease models, such as congestive heart failure and diabetes mellitus, both characterised by systemic inflammation and physical inactivity, a decreased oxidative capacity of skeletal muscle is also associated with a decreased expression of PGC-1α, PPAR-α and PPAR-δ, mRNA suggesting a prominent role for inflammation and physical activity level in controlling PPAR and PGC-1α levels [27–29]. Furthermore, it would be interesting to investigate PPAR and PGC-1 expression levels at different stages of COPD to increase insight in the aetiology and pathological mechanisms governing the observed decrease in skeletal muscle oxidative capacity in COPD patients.

PPARS AND REGULATION OF SKELETAL MUSCLE FUNCTION

Inflammation

Systemic inflammation is an important factor in the pathogenesis of weight loss and muscle wasting [30–32]. Many inflammatory responses are mediated by signalling through NF-κB. In its inactive form, NF-κB is bound to its inhibitor IκBα and is located in the cytosol. After activation, NF-κB is released

and translocates to the nucleus, where it initiates the transcription of its target genes, including those encoding inflammatory mediators [33]. NF-κB activation *per se* is sufficient for the induction of muscle atrophy [34]. Conversely, inhibition of NF-κB restored muscle mass in a number of experimental atrophy models including denervation and cancer cachexia [34]. Interestingly, NF-κB activation has been shown in skeletal muscle of severely underweight COPD patients by decreased content of IκBα and increased DNA binding of NF-κB [35]. Data regarding expression of inflammatory genes in relation to NF-κB activation are, however, lacking. Furthermore, some studies reported increased levels of inflammatory markers, including tumour necrosis factor (TNF)-α protein, in skeletal muscle of COPD patients [36, 37], while others did not [38]. This discrepancy may be related to differences in COPD phenotypes and muscles studied. Additional studies measuring inflammatory mediators in skeletal muscle of different COPD phenotypes (cachectic *versus* noncachectic) are needed to elucidate the exact implication of inflammatory signalling in the process of skeletal muscle wasting and cachexia in COPD.

Potent anti-inflammatory properties have been described for different PPAR isoforms. It was shown that specific PPAR-α activators effectively reduced NF-κB activation and re-established control over pro-inflammatory cytokine production, such as interleukin (IL)-6 and TNF-α, in various mouse tissues [39]. In addition, PPAR-α activators were found to induce expression of IκBα in primary smooth muscle cells [40]. PPAR-γ may also play an important role in the regulation of inflammation. Several PPAR-γ ligands have been shown to possess anti-inflammatory properties. For example, 15d-PGJ_2 was shown to inhibit matrix metalloproteinase-9, IL-1β, IL-6 and TNF-α production by human monocytes/macrophages [41, 42]. The TZD troglitazone decreased plasma levels of TNF-α in obese human subjects and effectively reduced nuclear localisation of NF-κB in mononuclear cells, suggesting a reduction in NF-κB mediated transcription [43]. Besides inhibition of nuclear translocation, PPAR-γ activation can also interfere with NF-κB signalling by a mechanism involving competition for transcriptional cofactors [44]. Furthermore, PPAR-γ activation can repress NF-κB activity by reducing NF-κB DNA-binding activity and preventing IκBα degradation [45]. Reports on anti-inflammatory effects of PPAR-δ are scarce. However, a recent study showed that PPAR-δ activation in C2C12 mouse skeletal muscle cells displayed anti-inflammatory properties [46].

In summary, convincing data implicate inflammation as a trigger of cachexia, which may be modulated by systemic delivery of PPAR agonists by suppressing inflammatory and subsequent atrophy signalling in skeletal muscle (fig. 1).

Oxidative stress

Development and progression of skeletal muscle atrophy in COPD has also been associated with an imbalance between reactive oxygen species (ROS) production and antioxidant capacity [47, 48]. Oxidative stress is present systemically as well as locally in skeletal muscle of COPD patients [49]. Experimental studies have shown that ROS can increase muscle proteolysis, inhibit muscle-specific protein expression and increase muscle cell apoptosis [50–52]. Moreover, several studies demonstrated that markers of nitrosative stress are also enhanced in skeletal muscle of COPD patients. Inducible nitric oxide synthase expression and/or nitrotyrosine formation were found to be enhanced in skeletal muscle of COPD patients in several independent studies suggesting that, in addition to oxidative stress, skeletal muscle is also exposed to nitrosative stress, which may also contribute to the process of protein degradation [35, 37, 53]. In contrast, it has been shown that nitric oxide (NO), at modest concentrations (*i.e.* when it appears to act as a signalling molecule causing reversible post-translational modifications), stimulates the formation of metabolically active new mitochondria through activation of the AMPK/SIRT1/PGC-1α/PPAR-δ signalling pathway [54, 55]. Based on the latter, it cannot be excluded that NO may serve to counteract mitochondrial dysfunction in conditions characterised by muscle degeneration, such as COPD, and further studies are necessary to properly address this issue.

A bulk of evidence points towards an inhibitory and attenuating effect of PPAR-α on oxidative stress. PPAR-α agonists can directly attenuate oxidative stress by preventing ROS generation, as it was shown that PPAR-α activation in mice restored impaired cellular redox balance, evidenced by a lowering of tissue lipid peroxidation and elimination of constitutively active NF-κB [39]. Furthermore, PPAR-α activation by fish oil feeding and fenofibrate administration to mice downregulated hydroxysteroid markers of ROS production in the liver [56]. Several studies demonstrated that activation of PPAR-α *in vivo* also causes an upregulation in a number of antioxidant enzymes, including catalase, copper(II) and zinc(II) superoxide dismutase (SOD) and mediators of the glutathione

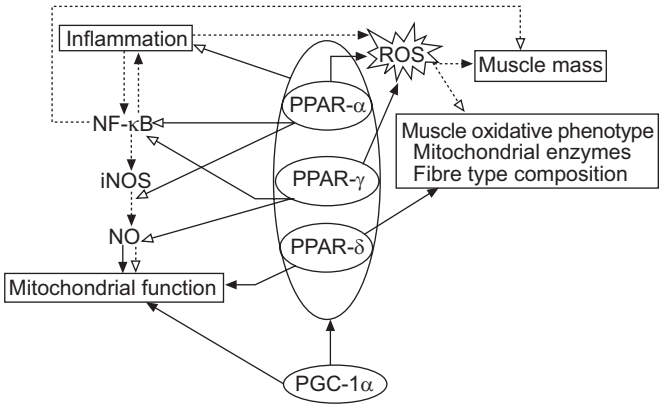

FIGURE 1. Negative effects of inflammation, and oxidative and nitrosative stress on muscle mass and oxidative phenotype, and the different levels of modulation by peroxisome proliferator-activated receptors (PPARs). Inflammation, oxidative and nitrosative stress negatively affect muscle mass and oxidative capacity. Different PPAR subtypes inhibit inflammatory signalling and oxidative and nitrosative stress at the indicated levels and may prevent or restore loss of muscle mass and oxidative phenotype. In addition, PPAR-δ and PPAR-γ co-activator-1α (PGC-1α) positively modulate muscle mass and oxidative phenotype and may oppose the effects of inflammation and oxidative-nitrosative stress. NF-κB: nuclear factor-κB; iNOS: inducible nitric oxide synthase; NO: nitric oxide; ROS: reactive oxygen species. ·····: negative effect on muscle mass and/or muscle oxidative phenotype; ——: positive effect on muscle mass and/or muscle oxidative phenotype; open arrowheads: inhibitory signal; filled arrowheads: stimulatory signal.

pathway [57]. More recent research confirms previous reports that PPAR-α activation in rats increases the antioxidant capacity and thereby modulates the oxidant–antioxidant balance in favour of the latter [58, 59]. In addition, cardiac-specific PPAR-α deficiency was accompanied by a decrease in cardiac manganese SOD expression and activity, and a subsequent increase in oxidative/nitrosative damage [60]. Besides PPAR-α agonists, PPAR-γ agonists are also able to reduce ROS formation [61, 62]. Two different PPAR-γ ligands were found to increase catalase mRNA expression and activity in endothelial cells [63]. Furthermore, glutathione and ascorbic acid levels in the hearts of diabetic rabbits were increased after PPAR-γ activation when compared with diabetic nontreated animals [64]. The exact mechanisms involved in the reduction of oxidative stress by PPAR-α and PPAR-γ agonists remain elusive.

Oxidative stress has been demonstrated consistently in skeletal muscle of COPD patients [53]. As PPAR activation diminishes oxidative stress in multiple tissues, it is reasonable to expect similar effects in skeletal muscle, which may be beneficial in alleviating skeletal muscle dysfunction in COPD.

Oxidative metabolism

A decrease in the type I slow oxidative muscle fibres and a concomitant increase in type II fast-twitch glycolytic fibres is reported in peripheral skeletal muscles of COPD patients, indicative of a relative shift from oxidative to glycolytic capacity [65]. As type II muscle fibres have a lower resistance to fatigue, this fibre-type shift may result in reduced endurance, as observed in peripheral skeletal muscle of COPD patients. According to this fibre-type shift, analyses of enzyme activities also reveal an overall increase in glycolytic and decrease in oxidative activities in peripheral skeletal muscles of these patients affecting muscle substrate metabolism [6, 66].

Expression of muscle genes that promote selective utilisation of lipid substrates is augmented during physiological states that are associated with increased systemic delivery of free fatty acids, such as exercise. Interestingly, many of the same muscle genes are also upregulated by *in vivo* administration of PPAR-α activators. It is observed that PPAR-α protein content is increased by exercise training and induced during myocyte differentiation, two conditions characterised by an increase in oxidative capacity [67, 68]. In addition, PPAR-α regulates fatty acid utilisation and expression of several genes involved in fatty acid β-oxidation in primary human skeletal muscle cells. [69]. Skeletal muscle expresses high levels of PPAR-δ and activation of the δ-subtype increases fatty acid β-oxidation, as well as mRNA levels of several classical PPAR-α target genes in both rodent and human skeletal muscle cells [70]. Overexpression of PPAR-δ in C2C12 myotubes resulted in an increment in fatty acid oxidation after activation by a synthetic ligand [71, 72]. In addition, analysis of rat myotubes treated with the PPAR-δ subtype selective agonist, GW 501516, revealed that PPAR-δ controls fatty acid oxidation by regulating genes involved in fatty acid transport, β-oxidation and mitochondrial respiration [73, 74]. These results, showing a significant overlap in the functions of PPAR-α and -δ, indicate that both subtypes play an important role in mediating lipid-induced regulation of oxidative pathways.

A recent study examining mice overexpressing PPAR-δ in muscle showed that the number of succinate dehydrogenase (SDH)-positive fibres (as a measure for oxidative fibres) was considerably increased in various muscles. This remodelling was due to hyperplasia and/or conversion of SDH-negative to -positive fibres, similar to what is observed upon endurance training [71, 75]. These histological observations were confirmed by the finding that muscle-specific PPAR-δ overexpression led to an increase of other oxidative enzymes, such as citrate synthase and β-hydroxyacyl-coenzyme A dehydrogenase. In addition, mitochondrial biogenesis was also enhanced. Conversely, activities of glycolytic enzymes remained unchanged [75]. Conversion of glycolytic fibres to oxidative fibres has also been reported in genetically altered animals that overexpress PGC-1α, which is a PPAR co-activator and a master regulator of mitochondrial biogenesis. Notably, putative type II muscles from PGC-1α transgenic mice also express proteins characteristic of type I fibres, such as troponin I (slow) and myoglobin, and show a greater resistance to fatigue. These data indicate that, in addition to PPAR-δ, PGC-1α is also a principal factor regulating muscle fibre-type determination and skeletal muscle exercise capacity [76].

Given the strong involvement of the PPARs and PGC-1α in regulation of skeletal muscle oxidative phenotype, the fact that skeletal muscle oxidative phenotype is impaired in COPD and the observation of reduced PPAR expression levels in skeletal muscle of COPD patients, it is tempting to suggest a possible therapeutic role for PPAR activators in muscle metabolism in COPD.

HOW CAN PPAR ACTIVITY BE MODULATED IN COPD?

COPD management requires an integrated approach aimed at pulmonary and extrapulmonary manifestations. In addition to therapies aimed at alleviating the primary lung impairment, evidence is accumulating that therapies targeting skeletal muscle dysfunction have a significant positive effect on quality of life and may even improve survival. Experimental studies have shown that PPAR-α and PPAR-γ can exert anti-inflammatory effects in the pulmonary compartment, which, with additional research, may translate into an interesting therapeutic avenue in the context of COPD lung pathology [13, 66, 67]. Moreover, based on the evidence described in the present article, it is tempting to suggest that a reduced content and activity of the PPARs may underlie some of the muscular disturbances in COPD. Nutritional intervention and exercise may positively influence PPAR content and activity in skeletal muscle. Indirect support for this notion is the beneficial effect of pulmonary rehabilitation on mitochondrial (fat) oxidative capacity and hence on skeletal muscle function in skeletal muscle of COPD patients [77]. PUFAs are common components of fatty fish and olive oil and are known PPAR activators. Interestingly, a recent randomised clinical trial showed that nutritional supplementation with PUFAs as adjunct to exercise training in COPD patients markedly enhanced exercise capacity compared with the placebo-treated group [78]. Several aspects of intervention with PPAR activators must be kept in mind. Two different aspects must be kept in mind. First, the positive influence of PPAR activators on skeletal muscle oxidative capacity and, secondly, the potent anti-inflammatory capacities of these agents. Concerning the effects on muscle oxidative capacity, the

rationale would be to introduce PPAR activators clinically to patients for whom daily life activities are limited by the decreased oxidative capacity of their lower limb skeletal muscles. Conversely, PPAR activators can be used to alleviate inflammatory status of COPD patients, for example, after exacerbations or in late-stage COPD to ameliorate the systemic inflammatory process. In addition, it is conceivable that PPAR agonists can delay or inhibit disease-specific processes, such as inflammation, if applied at early stages of disease development.

In conclusion, single or combined peroxisome proliferator-activated receptor agonists may represent a novel class of pharmacological agents that could be helpful in the management of chronic obstructive pulmonary disease.

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