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Roles of Peroxisome Proliferator-Activated Receptor β/δ in skeletal muscle physiology

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Abstract

More than two decades of studying peroxisome proliferator-activated receptors (PPARs) has led to an understanding of their implications in various physiological processes that are key for health and disease. All three PPAR isotypes, PPARα, PPARβ/δ, and PPARγ, are activated by a variety of molecules, including fatty acids, eicosanoids and phospholipids, and regulate a spectrum of genes involved in development, lipid and carbohydrate metabolism, inflammation, and proliferation and differentiation of many cell types in different tissues. The hypolipidemic and antidiabetic functions of PPARα and PPARγ in response to fibrate and thiazolidinedione treatment, respectively, are well documented. However, until more recently the functions of PPARβ/δ were less well defined, but are now becoming more recognized in fatty acid metabolism, energy expenditure, and tissue repair. Skeletal muscle is an active metabolic organ with high plasticity for adaptive responses to varying conditions such as fasting or physical exercise. It is the major site of energy expenditure resulting from lipid and glucose catabolism. Here, we review the multifaceted roles of PPARβ/δ in skeletal muscle physiology.

1. Introduction

Skeletal muscle, which is under voluntary control and whose function is to produce motion, is the most massive metabolic organ, comprising ~40% of total human body mass in a healthy individual [1]. It serves as the major site of glycogen storage, insulin-mediated glucose use, lipid metabolism and fatty acid oxidation [2-4]. Skeletal muscle consists of heterogeneous cell populations such as myocytes, stem cells and fibroblasts, and are enriched with blood supply and nerve endings. Myocytes form from the fusion of proliferating and differentiating myoblasts during myogenesis. They consist of slow- and fast-twitch fiber types that differ in the composition of contractile proteins, oxidative capacity, and substrate use for ATP production [5]. Skeletal muscle has high plasticity in tissue remodeling on demand such as occurs with fasting and exercise. During aging there is progressive loss of muscle mass and function, called sarcopenia, which also occurs in muscle disease. Furthermore, metabolic disorders, such as obesity and diabetes, which are characterized by excess calorie intake and impaired fatty acid oxidation and glucose use, cause muscle fiber type switching from slow- to fast-twitch fibers (type 1 to type 2b) [6, 7] (Table 1). Physical exercise helps in maintaining lipid homeostasis, and enhancing glucose uptake and expenditure and also leads to changes in fiber type composition from glycolytic (type 2b/x) to slow/fast oxidative (type 1/2a) fibers [8].

The regulatory roles of the Peroxisome Proliferator Activated Receptors (PPARs) are well recognized in preventing metabolic disorders and in muscle adaptation to fasting and physical exercise [9-17]. PPARs belong to the nuclear receptor superfamily of transcription factors, which comprises 48 members in human [9, 17]. Nuclear receptors have in common their ability to be activated by lipophilic ligands, which according to the receptor type can be

molecules such as lipids, retinoids, steroids, or thyroid hormones [18]. Many nuclear receptors are expressed in skeletal muscle, as well as in other organs often with circadian rhythmicity, including PPARα, PPARβ/δ, and PPARγ, the three isotypes that form the PPAR subfamily. Of note, all three PPAR isotypes show circadian rhythmicity in liver, but not in muscle. In addition, PPARα is rhythmic in both white adipose tissue (WAT) and brown adipose tissue (BAT), whereas, PPARγ is rhythmic in WAT and PPARβ/δ in BAT [19]. PPARs are critical regulators of genes involved in development, metabolism of lipids and carbohydrates, inflammation. They are also implicated in the proliferation and differentiation of several cell types in different tissues and their repair and regeneration following injury [10].

PPARs are activated by a variety of molecules, including fatty acids, fatty acid metabolites, non-metabolizable fatty acid derivatives, eicosanoids, phospholipids, and all-trans-retinoic acid for PPARβ/δ. PPARα, and PPARγ are the targets of synthetic molecules such as fibrates, and thiazolidinediones used as hypolipidemic and insulin-sensitizing drugs, respectively. Many other synthetic ligands, agonists, antagonists, and dual- and pan-agonists serve as useful tools to explore the functions of PPARs [15, 16]. PPARs heterodimerize with retinoid X receptors (RXRs) and bind to specific sequences on the DNA known as peroxisome proliferator response elements (PPRE) in the vicinity of the gene regulatory region (Fig. 1). PPARs stimulate target genes by recruiting co-activators, and histone acetylase complexes or alternatively, can inhibit gene expression by governing the assembly of co-repressor and histone deacetylase complexes. Posttranslational modifications such as phosphorylation, SUMOylation, and ubiquitination, and specific protein-protein interactions also participate in these regulatory mechanisms [20-26]. Thus, the PPAR-associated transcriptional machinery reflects the

complexity of the mechanisms involved in maintaining tissue homeostasis, the deregulation of which leads to pathological conditions.

Even though all three PPAR isotype genes are located on different chromosomes, they are often coexpressed at variable levels in different tissues with possible compensatory or complementary roles, including skeletal muscle where they exert specialized or pleiotropic responses [19, 27-29]. PPARα is highly expressed in tissues with active fatty acid catabolism, such as liver, heart, kidney, brown fat, intestine, macrophages, and muscle [9, 30]. It modulates all three fatty acid oxidation systems, viz. peroxisomal and mitochondrial β-oxidation and microsomal ω-oxidation, and plays a key role in lipid metabolism and energy expenditure [31, 32]. PPARγ, expressed as the two isoforms PPARγ1 and PPARγ2, is predominantly present in adipocytes and plays a crucial role in adipogenesis. Furthermore, PPARγ1 is found in other tissues such as breast, placenta, colon, liver, brain, macrophages and vascular cells [33-35]. PPARβ/δ has multifaceted roles and is expressed in all organs at various levels, where it can have a function in development, lipid metabolism, energy expenditure, tissue repair and regeneration, and inflammation [15, 27, 28, 36-38]. In recent years, PPARβ/δ has emerged as a key transcription factor in skeletal muscle biology. This review discusses the main contributions of PPARβ/δ to skeletal muscle physiology.

2. PPARβ/δ in skeletal muscle metabolism

Of the three PPARs, PPARβ/δ is the predominantly expressed isotype in skeletal muscle [19]. It is involved in multiple tasks comprising lipid metabolism, mitochondrial function promoting fuel use, and muscle fiber type changes associated with increased performance [2, 39-41] (Fig. 2). Genes involved in these functions have been identified as PPARβ/δ target genes.

The functions of PPARβ/δ in muscle cells have been studied in cell cultures, mainly mouse C2C12 myoblasts, rat L6 myoblasts, and human primary myotube cultures, after treatment with either natural (fatty acids) or synthetic (GW501516, GW0742) PPARβ/δ ligands, and in PPARβ/δ loss-of-function and gain-of-function animal models.

Cell culture work has shown that agonist-activated PPARβ/δ enhances fatty acid oxidation in skeletal muscle cells [2, 42]. It is also involved in mitochondrial biogenesis [2, 42-44] Furthermore, PPARβ/δ enhances the expression of FoxO1, a transcription factor involved in metabolic adaptation, with a parallel increase in PDK4, CD36, and lipoprotein lipase [45]. Increased PDK4 activity is known to inactivate the pyruvate dehydrogenase complex, which is rate limiting in muscle carbohydrate oxidation, resulting in up-regulation of fatty acid β-oxidation. Therefore, this pattern would be expected to promote use of fatty acids by the muscle and spare glucose for tissues that are more dependent on it, an adaptation that is particularly efficient during fasting (Fig. 2). This pathway was confirmed by the administration of the PPARβ/δ agonists GW0742 to rats and GW501516 to mice, which also triggered a switch in fuel metabolism to increased lipid catabolism and decreased carbohydrate utilization [46, 47].

Mice undergoing endurance exercise show an accumulation of PPARβ/δ protein in muscle [48]. Further, muscle-specific overexpression of PPARβ/δ in mice enhances muscle metabolism (fatty acid flux and β-oxidation) and remodels muscle fiber type to increase oxidative type 2a but not type 1 fibers. These mice also show decreased body fat mass and thus have smaller fat cells [48]. Interestingly, PPARβ/δ transgenic mice additionally display increased glucose metabolism. Together, these results from Luquet *et al.*, implicate PPARβ/δ in muscle development and adaptive response to exercise training. Another model is a mouse engineered to express in skeletal muscle a constitutively activated form of PPARβ/δ (VP16-PPARβ/δ) [49, 50].

These mice present increased numbers of type 1 muscle fibers with, unexpectedly, no change in PGC1α expression. They also have decreased adiposity and the ability to perform continuous running over twice the distance and time of non-engineered mice [49, 50]. When this activated form of PPARβ/δ is expressed in adipose tissue specifically it increases fatty acid oxidation and energy dissipation, resulting in reduced fat mass, better lipid profiles, and reduced adiposity and resistance to a high-fat diet [50]. Collectively, these PPARβ/δ transgenic mice appear to mimick, as far as fiber type composition is concerned, Calcineurin-, PGC1α-, Phosphoenolpyruvate-, and ERRγ-overexpressing transgenic mice, as well as Calsarcin-2-null mice [51-57]. Interestingly, it was also found that, in skeletal muscle, PPARβ/δ prevents endoplasmic reticulum stress-associated inflammation and insulin resistance through the activation of AMPK and subsequent inhibition of ERK1/2 signaling or through lysophophatidylcholines [58, 59]. Furthermore, it is noteworthy that the combined treatment with both the AMPK activator AICAR and the PPARβ/δ agonist GW0742 potentiates the effect of exercise in trained mice [58-60].

In contrast, muscle-specific deletion of PPARβ/δ in mice has revealed impaired fatty acid metabolism, decreased PGC1α expression, and muscle fiber type switching to a lower oxidative capacity [61]. These observations suggest a role of PGC1α as a target of PPARβ/δ. In fact, there is a PPRE in the promoter of the PGC1α gene as well as a cAMP response element and a myocyte-specific enhancer factor (MEF) binding site [61] (Fig 1). As already mentioned, exercise increases the level of PPARβ/δ protein and PPARβ/δ ligands (fatty acids), resulting in increased PPARβ/δ transcriptional activity, which stimulates expression of PGC1α. In turn, PGC1α acts as a co-activator of MEF2 and PPARβ/δ, promoting a positive feed-forward loop that increases PGC1α expression [61]. As a co-activator, PGC1α potentiates PPARβ/δ:RXR complexes, enhancing the expression of fatty acid uptake and β-oxidation genes (Fig. 1 and 2).

However, it is noteworthy that PGC-1α can also regulate oxidative metabolism in skeletal muscle independently of PPARβ/δ in sedentary mice fed a chow diet [62].

Similarly as for PPARβ/δ:RXR, PGC1α serves as a co-activator of nuclear respiratory factor 1 (NRF1) and NRF2, resulting in increased expression of nuclear-encoded mitochondrial genes (Fig. 1). Furthermore, PGC1α also co-activates MEF2, stimulating expression of slow-twitch muscle fiber genes and the switch to type 1 fibers [61, 63] (Fig. 2). Interestingly, PPARβ/δ and PPARα exert opposing actions on the type 1 fiber program through a muscle microRNA network, involving miR-499 and miR-208b, which depends on the action of the estrogen-related receptor γ (ERRγ) [64] .

Muscle-specific PPARβ/δ-deficient mice present a significant increase in body weight with a regular or high-fat diet as a result of enhanced body fat content and increased adipocyte size in WAT. During aging, these mutant mice display increased adipocyte hypertrophy, insulin resistance, and glucose intolerance [61]. The development of this phenotype is reminiscent of the development of obesity and diabetes in both humans and mice. Interestingly, liver-specific PPARβ/δ knockout mice also show impaired lipid use in skeletal muscles as a result of decreased fatty acid uptake and handling suggestive of inter-organ crosstalk [65]. Therefore, it would be of interest to explore any alterations in the levels of hepatomyokines such as FGF21, IGF1, Irisin, Myostatin and Myonectin. Furthermore, it would be important to investigate whether the circadian regulation of metabolism is perturbed in these mice because PPARs are clock-controlled, and the controlling genes and PPARβ/δ might be a target for mir-122 [66].

3. PPARβ/δ in skeletal muscle plasticity

As described above, muscle-specific PPARβ/δ overexpression or expression of a constitutively active VP16-PPARβ/δ protein in transgenic mice has revealed a role for this nuclear receptor in muscle remodeling with increased succinate dehydrogenase (SDH) positive fibers in soleus and tibialis anterior muscles, indicating a fiber type switch from fast glycolytic 2b to slow/fast oxidative 1/2a fibers [48, 49] (Table 1). This switch results in decreased fat mass and adipocyte size, similar to the effects of endurance training in mice and humans, with resistance to fatigue [48-50] (Fig. 3). In fact, exercise training shifts muscle fiber types from anaerobic fast glycolytic (type 2b) to aerobic slow/fast oxidative (type 1/2a) metabolism [62-64]. This fiber type change is associated with increased mitochondrial number, capillary density and myoglobin levels, and the fibers thus look red [48, 50, 67-69] (Table 1). Furthermore, physical exercise enhances PPARβ/δ expression and improves cardiorespiratory fitness and decreases circulating lipids levels. In parallel with decreased liver fat accumulation and inflammatory markers, enhanced glucose uptake associated with physical exercise also is observed. Moreover, the type and duration of exercise determines muscle mass or hypertrophy [70, 71].

Obviously, muscle-specific overexpression of PPARβ/δ and its pharmacological activation with synthetic agonists in sedentary mice phenocopies some of the effects of physical exercise, including increased capillary-to-fiber ratio with increased VEGF-A and PECAM-1. Activated PPARβ/δ generates new myofibers (hyperplasia), with increased myonuclear density because of enhanced Myf5 and MyoD1 expression levels in transgenic mice. Increased Myf5 and MyoD1 indicates that satellite stem cells might be activated, leading to enhanced proliferation and differentiation of muscle precursor cells into new myofibers [72-77]. Interestingly, the age-related loss of myonuclear density can be restored in mice treated with PPARβ/δ agonists [78].

Furthermore, MyoD in association with alternative NF-kB transcription factor RelB occupies multiple sites on *Pparβ/δ* and *Pgc1β,* but not *Pgc1α,* promotor regions and regulates oxidative metabolism of adult skeletal muscle in mice [79].

Physical inactivity leads to increased glucose circulating in blood, enhanced visceral adiposity, and decreased postprandial lipid clearance. Physical inactivity also results in decreased muscle mass and the development of obesity and diabetes over time and with increasing age [80]. Loss of PPARβ/δ in muscle stem cells or globally in mice is associated with decreased satellite stem cell number and proliferation rate. Muscle regeneration following cardiotoxin muscle injury is impaired in mice with stem cell PPARβ/δ deficiency, and these animals also have decreased myonuclear density. PPARβ/δ seems to play a role for the normal sequence of events after injury [81, 82]. In addition, the global deletion of PPARβ/δ in mice results in decreased body and hind limb muscle weights postnatally because of the increased muscle atrophy [82]. In contrast, activation of PPARβ/δ with agonists enhances the potential of muscle precursor cell differentiation *in vitro* [83]. As already mentioned, the muscle-specific deletion of PPARβ/δ in mice mimics some of the effects of physical inactivity, such as impaired fatty acid metabolism and glucose intolerance [61, 81].

Sarcopenia is characterized by a progressive loss of muscle mass, leading to frailty and frequent falls and increasing morbidity, and can be a causative factor in mortality. During healthy aging, the muscle fibers shift from fast glycolytic to slow oxidative fiber types (type 2x to type 1) in humans as an adaptation for slow and sustained movements and to meet postural demands [84]. However, the expression levels of PPARβ/δ is reduced during aging [85]. Interestingly, females have a higher percentage of slow oxidative fibers (type 1) compared to males, possibly because of an evolutionary adaptation to specific needs and female hormone

specific conditions [86]. It would be interesting to know the significance of the fiber type switch during healthy aging and the sex-specific prevalence of slow oxidative fibers from the perspective of potential PPARβ/δ effects. Finally, it is not known whether deletion of PPARβ/δ induces some so far unknown compensatory effects by the two other PPAR isotypes in muscle. One way to address these potential compensatory effects as well as inter-organ crosstalk is to generate muscle-specific PPARα, PPARβ/δ, and PPARγ double or triple knockout mice.

Collectively, the results presented above underscore the crucial role of PPARβ/δ in muscle physiology, particularly in the challenging conditions of fasting and sustained physical activity. In sum, PPARβ/δ contributes in a major way to muscle plasticity.

3. PPARβ/δ in skeletal muscle disorders

Our knowledge is limited about the implications of PPARβ/δ activation in muscle disorders such as inherited fatty acid oxidation defects, myopathies and muscular dystrophies. Pharmacological activation of PPARβ/δ by hypolipidemic agents such as bezafibrate improves fatty acid oxidation in patients suffering with fatty acid oxidation defects due to partial activity loss of the CPT-2 and VLCAD enzymes [87, 88]. In addition, the pharmacological activation of PPARβ/δ in rats appeared to activate a muscle atrophy programme, possibly through modifications in the Akt1/FOXO/MAFbx and MuRF1 signalling pathway [46]. However, this effect has not been studied further. Furthermore, activation of PPARβ/δ stimulates mitochondrial respiration through increased PGC1α, and increases the life span of COX10 mutant mice affected by mitochondrial myopathy [89]. Duchenne muscular dystrophy (DMD) is a genetic neurodegenerative muscle disease characterized by severe muscle wasting, leading to premature death. In clinical studies and the *mdx* mouse model of DMD, there is a higher susceptibility to

myofiber degeneration in glycolytic compared to oxidative fibers [90]. In mice, Utrophin A (an autosomal homologue of dystrophin), which is necessary for membrane maintenance and acetylcholine receptor clustering, decreases myofiber loss, which is greater in type 1/2a than type 2b/x fibers [91]. Activation of Utrophin A by calcineurin/NFAT signaling ameliorates the DMD phenotype in *mdx* mice [91]. Furthermore, activation of PPARβ/δ also improves the DMD phenotype in *mdx* mice by direct transcriptional activation through a PPRE in the Utrophin A promoter region [92]. Notably, the pharmacological activation of PPARβ/δ promotes calcineurin-dependent fiber remodeling in mice [72]. The calcineurin and its substrate NFAT-dependent pathway have been implicated in the regulation of Myf5 gene expression in the reserve cell population of myotubes [93]. Interestingly, the pharmacological activation of PPARβ/δ transiently increases the expression of Myf5. Complete blunting of PPAR agonist-mediated muscle fiber type remodeling by co-administration of cyclosporine A in mice suggests an indirect action through calcineurin pathway [72]. These findings suggest that pharmacological activation of the PPARβ/δ might be a potential treatment target in some of these muscle disorders. The signaling pathway(s) involved in the muscle fiber type remodeling have yet be unveiled.

Conclusions

In skeletal muscle, PPARβ/δ acts as a key regulator of fuel metabolism, promoting a shift from glucose to lipid as the main energy substrate. It promotes cellular lipid uptake, activation of fatty acids by fatty acyl CoA synthetase and their mitochondrial uptake and β-oxidation with decreased glucose oxidation as a consequence, which mimick fasting and physical exercise conditions. Pharmacological activation of PPARβ/δ in muscle phenocopies physical exercise in muscle remodeling, with a switch from glycolytic 2b/x to slow/fast oxidative 1/2a fiber types, an

increase in the capillary-to-fiber ratio, and the formation of new myofibers with increased myonuclear density. Finally, pharmacological activation of PPARβ/δ in mice results in an improved muscle phenotype in certain muscle disorders, such as inherited disorders of the fatty acid oxidation system, mitochondrial myopathy, and DMD. Collectively, the studies presented in this review show that activation of PPARβ/δ in skeletal muscle results in enhanced lipid metabolism as an adaptive response to external stimuli such as food availability and prolonged physical activity. Given that activation of PPARβ/δ in skeletal muscle enhances lipid use for energy expenditure, which is preferred to glucose and allows glucose to become more available for peripheral organs, PPARβ/δ could potentially be used as a therapeutic target for some muscle diseases. Finally, knowledge remains limited about circadian clock gene regulation by PPARβ/δ in peripheral organs and its impact on chrono-metabolism, and the role of PPARβ/δ in epigenetics and microRNA-mediated regulation of skeletal muscle metabolism and function. Clearly, much work remains to be done before any clinical PPARβ/δ-based interventions will be possible in muscle diseases.

Disclosure of potential conflicts of interest

The authors indicate no potential conflicts of interest

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Table 1. ***Skeletal muscle fiber types and their characteristics.***

Fiber properties	**Type 1**	**Type 2a**	**Type 2x/d**	**Type 2b**
Twitch/contraction	Slow	Moderate	Fast	Very fast
Myosin ATPase activity	Slow	Fast	Fast	Fast
MHC isoform	MHC1	MHC2a	MHC2x/d	MHC2b
ATP synthesis	Oxidative	Predominantly oxidative	Glycolytic	Glycolytic
Fatigue	Resistant	Moderately resistant	Fast fatigable	Very fast fatigable
Force production	Weak	Intermediate	Strong	Very high
Endurance capacity	High	Intermediate	Low	Low
Myoglobin content	High	High	Low	Low
Appearance	Red	Red	White	White
Capillaries density	High	High	Low	Low
Mitochondria numbers	High	High	Low	Low
Fiber size (CSA)	Small	Intermediate	Large	Large
Major fuel source	Triglycerides	Creatine phosphate, glycogen	ATP, creatine phosphate, glycogen	ATP, creatine phosphate,
Properties	Use lactic acid	Produce lactic acid, creatine phosphate	Use creatine phosphate	Use creatine phosphate
Motor neuron size	Small	Medium	Large	Very large
Rodents	Present	Present	Present	Present
Humans	Present	Present	Present	Undetectable

Figure legends

Fig. 1. PPARβ/δ in skeletal muscle metabolism and myofibers determination. Various stimuli and signalling molecules, such as physical exercise and fasting, fatty acids and synthetic ligand regulate the PPARβ/δ:RXR heterodimer formation and transcription activation or repression of PPARβ/δ target genes. The PPARβ/δ:RXR heterodimer binds to specific sequences on the DNA known as PPRE in the regulatory regions of target genes, such as *Pgc1α.* In turn, PGC1α acts as a co-activator of PPARβ/δ, NRFs and MEF2. AICAR, 5-aminoimidazole-4-carboxamide riboside; AMPK, 5' Adenosine monophosphate-activated protein kinase; PGC1α, PPAR gamma coactivator-1alpha; P, phosphorylation; PPARβ/δ, Peroxisome Proliferator-Activated Receptor beta/delta; RXR, Retinoid X Receptor; PPRE, Peroxisome Proliferator Response Element; CD36, Cluster of differentiation 36; LPL, Lipoprotein lipase; PDK4, Pyruvate dehydrogenase kinase 4; NRFs, Nuclear respiratory factors; MEF2, Myocyte enhancer factor 2; FOXO1, Forkhead box O1; MyoD, Myogenic differentiation

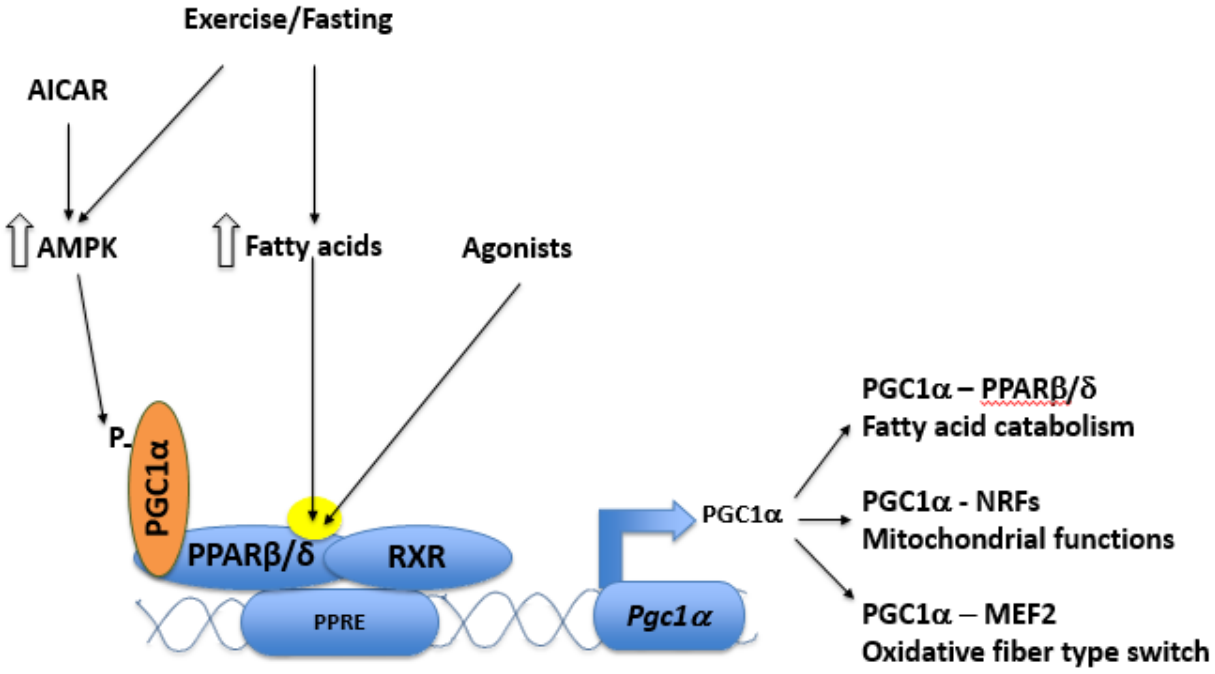

FIGURE 1

Fig. 2. Model of fasting and exercise-enhanced metabolic pathways and fiber type switching in skeletal muscle : a multifaceted role of PPARβ/δ. Fasting and exercise increase the expression of PPARβ/δ as well as the mobilization of fatty acids (FAs). FAs and synthetic ligands can activate the receptor. PPARβ/δ agonists increase the phosphorylation and expression of AMPK. Activated PPARβ/δ stimulates the expression of lipoprotein lipase (LPL) and CD36, increasing the flux of FAs into the muscle cells. It also stimulates the expression of pyruvate dehydrogenase kinase 4 (PDK4), which reduces glucose oxidation. PPARβ/δ stimulates the PGC1α gene via a PPRE in its promoter. In turn, PGC1α co-activates the PPARβ/δ:RXR heterodimers to enhance the expression of genes involved in FA β-oxidation. PPARβ/δ also stimulates the PGC1β gene independently of PGC1α through binding of MyoD and RelB and regulates mitochondrial biogenesis. By coactivating nuclear respiratory factors (NRFs), PGC1α increases the expression of nuclear mitochondrial genes. Furthermore, through coactivation of myocyte enhancer factor 2 (MEF2), PGC1α promotes the switch to the expression of slow twitch muscle fiber genes. The muscle fiber type/size and angiogenesis is further determined by PPARβ/δ target genes, such as FOXO, and VEGF-A and PECAM-1, respectively. AICAR, 5- aminoimidazole-4-carboxamide riboside; AMPK, 5' Adenosine monophosphate-activated protein kinase; FA, Fatty acids; LPL, Lipoprotein lipase; TAG, Triacylglycerol; FAT/CD36, Fatty acid translocase/Cluster of differentiation 36; FA-CoA, Fatty acyl coenzyme A synthase; PDK4, Pyruvate dehydrogenase kinase 4; Ac-coA, Acetyl coenzyme A, TCA, Tricarboxylic acid; PPARβ/δ, Peroxisome Proliferator-Activated Receptor beta/delta; FOXO1, Forkhead box O1; MAFbx, Muscle atrophy F-box/Atrogin1; MuRF1, Muscle RING-finger protein-1; PGC1α/β, PPAR gamma coactivator-1alpha/beta; MEF2, Myocyte enhancer factor 2; NRF, Nuclear respiratory factor; MyoD, Myogenic differentiation 1; RelB, Reticuloendotheliosis viral oncogene homolog B/NF-kB, Nuclear factor kappa light polypeptide gene enhancer in B-cells 3; VEGF-A, Vascular endothelial growth factor A; PECAM-1, Platelet and endothelial cell adhesion molecule 1.

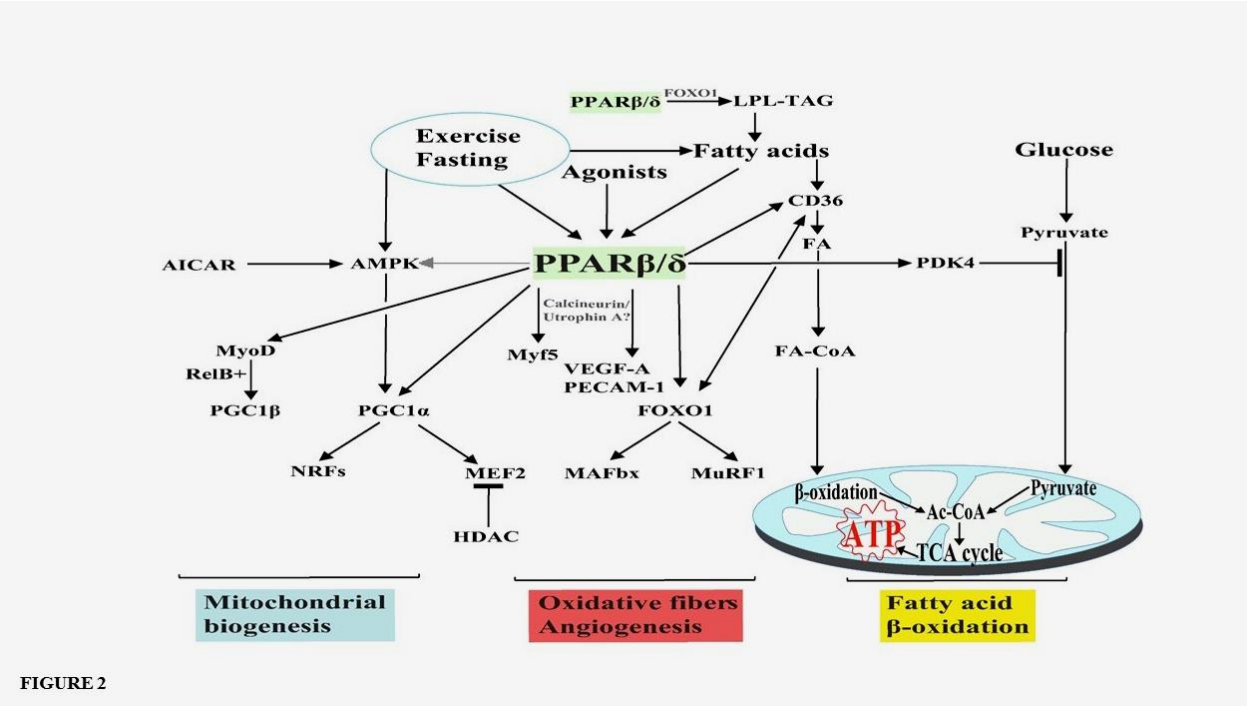

FIGURE 2

Fig. 3. Activation of PPARβ/δ phenocopies fasting and exercise-mediated skeletal muscle remodeling and physiology. In the healthy animal, pharmacological activation of PPARβ/δ produces effects similar to those of exercise or fasting. Muscle-specific deletion of PPARβ/δ triggers a fiber-type switching toward lower oxidative fibers; this switching is followed by the development of obesity and diabetes. This model proposes that fiber-type switching is likely to be the cause and not the consequence of obesity and diabetes in the PPARβ/δ-deficient mice.

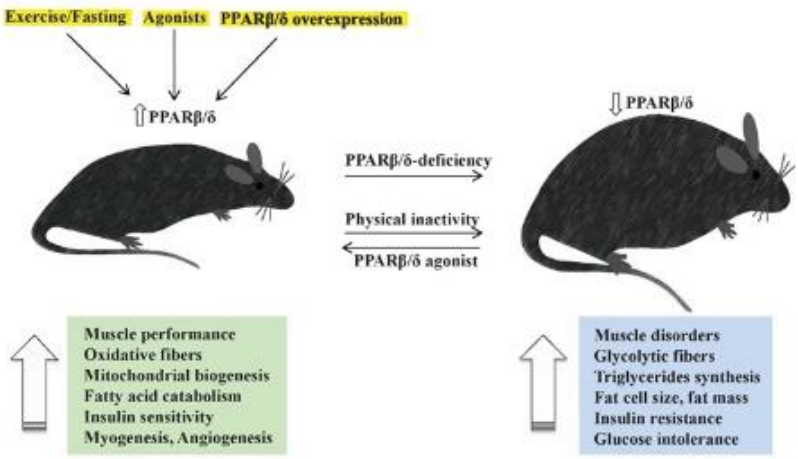

FIGURE 3