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Peroxisome proliferator-activated receptor β/δ: a master regulator of metabolic pathways in skeletal muscle

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Abstract

Skeletal muscle is considered to be a major site of energy expenditure and thus is important in regulating events affecting metabolic disorders. Over the years, both in vitro and in vivo approaches have established the role of peroxisome proliferator-activated receptor-β/δ (PPARβ/δ) in fatty acid metabolism and energy expenditure in skeletal muscles. Pharmacological activation of PPARβ/δ by specific ligands regulates the expression of genes involved in lipid use, triglyceride hydrolysis, fatty acid oxidation, energy expenditure, and lipid efflux in muscles, in turn resulting in decreased body fat mass and enhanced insulin sensitivity. Both the lipid-lowering and the anti-diabetic effects exerted by the induction of PPARβ/δ result in the amelioration of symptoms of metabolic disorders. This review summarizes the action of PPARβ/δ activation in energy metabolism in skeletal muscles and also highlights the unexplored pathways in which it might have potential effects in the context of muscular disorders. Numerous preclinical studies have identified PPARβ/δ as a probable potential target for therapeutic interventions. Although PPARβ/δ agonists have not yet reached the market, several are presently being investigated in clinical trials.

Keywords: fatty acid oxidation; lipid metabolism; muscle fiber switching; obesity; peroxisome proliferator-activated receptor-β/δ (PPARβ/δ).

Abbreviations

ABCA	ATP binding cassette
ACS	acyl-CoA synthetase
ADRP	adipocyte differentiation-related protein
AMPK	AMP-activated protein kinase
ApoE	apolipoprotein-E
COX	cytochrome c oxidase
CPT	carnitine-palmitoyl transferase
CS	creatine synthase
FABP/hFABP	heart fatty-acid binding protein
FAT/CD36	fatty acid translocase
GLUT4	glucose transporter 4
LCAD, MCAD, and SCAD	ong, medium and short-chain acyl-CoA dehydrogenase
LCAS	long chain acyl-CoA synthetase
LPL	lipoprotein lipase
MAFbx	muscle atrophy F-box
MuRF1	muscle ring finger 1
PDK	pyruvate dehydrogenase kinase
PFK	phosphofructokinase
PGC1α	peroxisome proliferator-activated receptor γ coactivator1α
SCD	stearoyl CoA desaturase
SREBP1c	sterol regulatory element binding protein-1c
UCP	uncoupling protein
β-HAD	β-hydroxy-acyl-CoA dehydrogenase

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Introduction

Skeletal muscle is considered to be the most abundant organ in the human body, comprising approximately 40% of the total body mass [1]. Because it is also the most active metabolically, it serves as the major site of fatty acid oxidation and lipid metabolism [2]. In addition, skeletal muscle plays a key role in the regulation of glucose use. In fact, skeletal muscles are thought to account for approximately 75% of insulin-stimulated glucose uptake [3, 4]. In obesity, insulin-stimulated glucose disposal is reduced in skeletal muscles [5–8]. Under these conditions, intramyocellular lipid content is increased, possibly resulting in the development of insulin resistance, a characteristic feature of chronic metabolic disorders such as type 2 diabetes [9–11]. This relationship underscores the importance of skeletal muscle in regulating events involved in metabolic disorders. Various molecular pathways, in which the regulatory roles of peroxisome proliferator-activated receptors (PPARs) are well recognized, have been associated with these disorders [12].

PPARs are members of the nuclear receptor superfamily and share the same structural organization as other family members [13]. They have a less-conserved ligand-independent activation domain (A/B) at the amino terminal end; a well-conserved DNA binding domain (C), consisting of two zinc finger-like structures comprising the α-helical DNA binding motif; a hinge region (domain D), implicated in interactions with cofactors; and a well-conserved ligand binding domain (LBD) at the C-terminal end (E/F domain) [14, 15]. The ligand-dependent activation function (AF-2)

resides within the LBD and enables heterodimerization of PPAR with its obligate retinoid X receptor (RXR) partner. The ligand-activated heterodimer binds to peroxisome proliferator response elements (PPREs) present in the control regions of the target genes, recruits coactivators, and stimulates transcription [16–19]. Thus, PPARs are lipophilic ligand-inducible transcription factors that form a subfamily comprising three subtypes: PPARα (NR1C1) [20], which can be activated by peroxisome proliferators (hence the name) [21], PPARβ/δ (NR1C2), and PPARγ (NR1C3) [22].

Although encoded in separate genes, the three PPARs are often coexpressed at variable levels in different tissues [23, 24]. PPARα is highly expressed in liver, kidney, heart, and skeletal muscles [24] and functions as a regulator for the uptake and oxidation of fatty acids, lipoprotein metabolism, and control of inflammatory responses [25, 26]. PPARγ is expressed predominantly in adipose tissue and regulates adipogenesis and fat storage and occurs in two isoforms, γ1 and γ2. The γ1 isoform is relatively abundant in preadipocytes and is also expressed at high levels in colon epithelium and in immune cells. PPARγ2 is the predominant isoform in preadipocytes and adipocytes [27], and apart from its role in adipocyte differentiation, is involved in a diverse array of other biological processes including insulin sensitization and cell differentiation [28]. PPARβ/δ is expressed ubiquitously [24] and is also implicated in different cellular functions in the skin [29], brain [30], adipose tissue, heart, skeletal muscle [12], and inflammation [31]. This isotype is particularly implicated in tissue repair [32] and energy expenditure [33], and its activation regulates dyslipidemia, resulting in improved serum lipid profiles [34–36]. This review discusses the roles of PPARβ/δ in the regulation of energy metabolism in skeletal muscles and the pathways through which it exerts its action.

Role in fatty acid metabolism

In addition to skeletal muscle, white and brown adipose tissues (WATs and BATs) significantly contribute to fatty acid metabolism and energy homeostasis [37, 38]. Excess energy is stored in the form of triglycerides in WATs, and in times of energy need it is released as free fatty acids and glycerol in circulation and further used mainly by BATs, skeletal muscle, and liver. BATs produce abundant heat from fatty acid oxidation by uncoupling the production of ATP from the electron transport chain. Apart from BATs, this process of energy dissipation also takes place in skeletal muscles. Thus, skeletal muscles play an important role in coordinating metabolic processes by regulating lipid and carbohydrate catabolism along with thermogenesis. Of importance, of the three isotypes, PPARβ/δ is the one that is predominantly expressed in skeletal muscles [39] and involved in these metabolic pathways [40].

The role of PPARβ/δ as a central regulator of fatty acid metabolism in skeletal muscles was established through different transgenic animal models with either muscle-specific overexpression [41, 42] or deletion of PPARβ/δ [43]. Germline PPARβ/δ-null animals have been difficult to obtain because of the placental defects observed during the midgestation period [44–46]. Probably because of these difficulties, which delayed the availability of null mice, the first study to report the involvement of PPARβ/δ in fatty acid oxidation was performed in primary cultures of human skeletal muscle myotubes, showing that polyunsaturated fatty acids regulate *ucp-2* expression through PPARβ/δ activation [39]. Experiments involving gain and loss of functions of PPARβ/δ further confirmed the regulatory role of this receptor in lipid metabolism in skeletal muscle cells [47]. C2C12 cells overexpressing PPARβ/δ and treated with a selective agonist increase the expression of genes involved in fatty acid oxidation (CPT-1), fatty acid uptake (FAT/CD36), and binding (FABP3 also called hFABP). A weak but significant dose-dependent increase in lipoprotein lipase (LPL) and acyl-CoA synthetase (ACS) mRNA levels has also been observed in these cells.

Furthermore, pharmacological activation of PPARβ/δ by a specific ligand (GW501516) alone or in combination with an agonist for RXR (LG101305) regulates genes involved in triglyceride hydrolysis and fatty acid oxidation, lipid use, energy uncoupling, and lipid efflux in differentiated myotubes [2]. When GW501516 or LG101305 are used separately, the response is moderate from the majority of investigated candidate target genes involved in skeletal muscle lipid and carbohydrate metabolism, such as CD36 and FABP3 (involved in fatty acid uptake and binding); SREBP1c and SCD1 and SCD2 (involved in lipogenesis); LPL, ACS4, and M-CPT1 (triglyceride hydrolysis and fatty acid oxidation); PDK4 (glucose use); ABCA1 and ApoE (lipid efflux); and adipophilin/ADRP (lipid storage). However, a high induction of the genes involved in thermogenesis and energy expenditure, such as uncoupling protein 1 (UCP1) and UCP2, results when the cells are treated with the PPARβ/δ ligand alone, and only UCP2 responds moderately to the RXR agonist alone. Of interest, most of these genes are synergistically upregulated on co-treatment with agonists for both receptors.

These observations suggested a potential collaboration between PPARβ/δ and RXR ligands in skeletal muscle cells with regard to metabolic pathways. This concept was further consolidated by another study in which a microarray analysis of GW501516-treated myotubes revealed that PPARβ/δ controls fatty acid oxidation by regulating genes involved in fatty acid uptake, fatty acid β-oxidation, and mitochondrial respiration [48]. In addition to the effect of GW501516 on myotubes, the role of PPARβ/δ in metabolic homeostasis in skeletal muscles was also confirmed in vivo. Effects similar to those mentioned above have been observed in skeletal muscles of mice treated with GW501516. More important, administration of GW501516 to mice fed a high-fat diet ameliorates diet-induced obesity and insulin resistance. These outcomes are accompanied by enhanced metabolic rate and fatty acid β-oxidation, an increased number of mitochondria, and a marked reduction in lipid droplets, indicating that the effects of the PPARβ/δ agonist on skeletal muscles might have a significant efficacy against diet-induced obesity. Furthermore, treatment with GW501516 prevents diabetes in

genetically obese *ob*/*ob* mice not only by affecting the change in body weight but also by significantly decreasing plasma glucose and insulin levels. Collectively, these observations thus suggest that the inducing effects of the PPARβ/δ agonist on fatty acid oxidation and energy expenditure result in amelioration of obesity and insulin resistance in obese animals, which might be of therapeutic significance.

In addition to in vivo activation of PPARβ/δ through a specific agonist, a study involving transgenic mice with muscle-specific overexpression of the receptor [41] has been performed to decipher the role of PPARβ/δ as a key target in metabolic disorders in skeletal muscles. Muscle-specific PPARβ/δ overexpression results in decreased body fat content without alteration in lean mass. A large reduction in the adipose pad weight resulting from a decrease in the adipocyte cell size has also been observed [41]. Thus, PPARβ/δ activation leads to increased lipid catabolism in muscle, thereby decreasing its accumulation in adipose tissue and resulting in beneficial effects in preventing disorders that result from fat accumulation. Apart from the increased PPARβ/δ activity through ligand activation or its overexpression, mice in which PPARβ/δ has been selectively ablated in myocytes further confirmed the pivotal role of the receptor in regulating metabolic pathways in skeletal muscles. Muscles in these mice have a lower oxidative capacity that precedes the development of obesity and diabetes [43]. Transcript levels are lower in these mutant mice for genes controlling lipolysis (LPL), fatty acid uptake (FAT/CD36), binding (hFABP/FABP3), activation (LCAS), and β-oxidation (LCAD, MCAD, SCAD, and β-HAD), the TCA cycle (CS), and UCP3, whereas two genes of the glycolytic pathway (PFK and GLUT4) remain unaltered, thus confirming once more that PPARβ/δ controls fatty acid metabolism in skeletal muscles. In comparison to their control littermates, the mutant mice show a significant increase in body weight when fed a high-fat diet and are insulin resistant and glucose intolerant. Even on a regular diet, these mutant mice gain more weight than do control animals. This increased body weight results from increased body fat content and increased adipocyte size in WATs but not from increased muscle weight. This phenotype is most probably a consequence of the impaired fatty acid breakdown resulting from deletion of PPARβ/δ, which results in increased fat storage in adipose tissue.

PPARβ/δ activation leads to muscle fiber switching

One of the roles of PPARβ/δ is to control the skeletal muscle fiber type composition [41, 42]. Depending on metabolic properties and type of myosin heavy chain, skeletal muscle fibers can be classified into type I (oxidative/slow) and type II (glycolytic/fast) fibers. The oxidative slow-twitch fibers have large amounts of mitochondria and high levels of myoglobin and mainly use oxidative metabolism to provide a stable and long-lasting supply of ATP; thus, they are fatigue-resistant [49, 50], whereas the fast-twitch glycolytic fibers have fewer mitochondria and rely on glycolytic metabolism as a major energy source and are fatigable [51–53].

PPARβ/δ overexpression leads to an increase in the percentage of type I fibers [41]. As a consequence, there is an increase of both enzymatic activity (CS and β-HAD) and expression of genes implicated in oxidative metabolism (UCP2, hFABP/FABP3). Moreover, a transgenic mouse with a constitutively active form of PPARβ/δ has been generated [42]. This mouse expresses a transgene in which the VP16 activation domain is fused to the N-terminus of full-length PPARβ/δ in an expression vector under the control of the human α-skeletal actin promoter, allowing expression specifically in skeletal muscles. Expression of this constitutively active form of PPARβ/δ results in a profound and coordinated increase in oxidation enzymes, mitochondrial activity (COXII, COXIV, UCP2, and UCP3), and production of characteristic type I fiber proteins, such as myoglobin and troponin I [42]. In addition, administration of the PPARβ/δ agonist GW501516 has similar effects, thus providing evidence that activation of endogenous PPARβ/δ affects fiber type composition towards an increased proportion of type I fibers. This effect of PPARβ/δ is mediated through its transcriptional coregulator PGC1α [43] (Figure 1). Mice with a skeletal muscle-specific PPARβ/δ deletion have a reduced level of PGC1α expression. In fact, there is a conserved PPRE in the promoter region of the PGC1α gene in both mouse and human, and PPARβ/δ agonist treatment stimulates the PGC1α promoter through this specific PPRE (Figure 1).

Previous studies have also reported PGC1α to be an important regulator of the maintenance of the slow-twitch muscle fiber type [54, 55]. Of interest, PGC1α exhibits a high level of expression in the slow-twitch oxidative muscles rather than the fast-twitch glycolytic fibers [55]. Also in humans, a high level of expression of both PPARβ/δ and PGC1α has been observed in biopsies from cyclists who generally have a high proportion of type I muscle fibers. A decrease in the expression of both is noted in patients with spinal cord injuries resulting in a loss of type I fibers [56]. Apart from PPARβ/δ and PGC1α, another important regulator implicated in the maintenance of muscle fiber composition is calcineurin [57, 58]. PPARβ/δ activation is associated with a calcineurin-dependent effect on muscle morphology that enhances the oxidative phenotype, thus suggesting the involvement of a calcineurin-dependent signaling pathway in PPARβ/δ-promoted muscle remodeling [59]. Moreover, the phenotype exhibited by transgenic mice expressing higher levels of calcineurin, calmodulin-dependent kinase, or PGC1α [60–62] is similar to that of mice overexpressing the activated form of PPARβ/δ in skeletal muscle [42], indicating a possible link between these signaling pathways.

PPARβ/δ-mediated muscle fiber transformation protects against obesity

There is a correlation between the composition of specific muscle fiber and the development of obesity and diabetes.

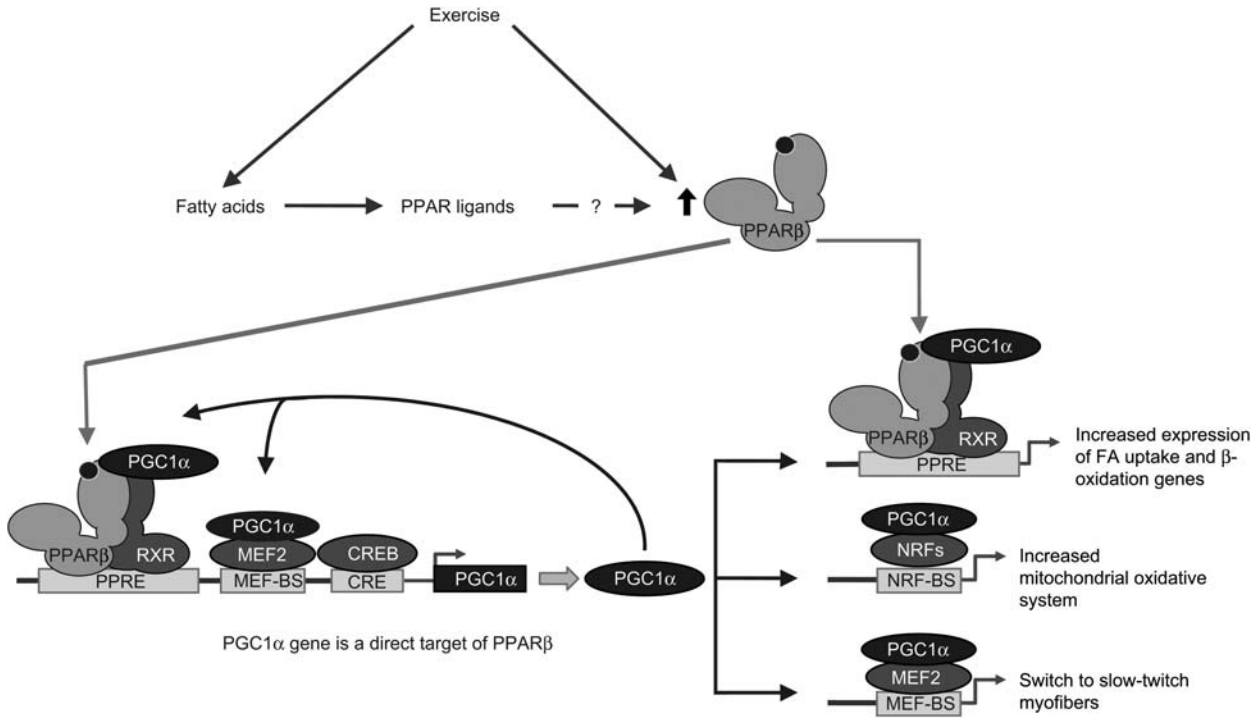

Figure 1 Model of exercise-induced metabolic pathways and fiber type switching in skeletal muscle cells.
The promoter of the PGC1α gene comprises a PPRE, a myocyte-specific enhancer factor (MEF) binding site (MEF-BS), and a cAMP response element (CRE). The PGC1α promoter is stimulated by muscle contraction that induces a calcium-signaling pathway, which activates CREB and MEF2 via Ca^{2+}/calmodulin-dependent kinase IV (CaMKIV) and calcineurin A. Exercise can increase the level of PPARβ/δ ligands (fatty acids) and furthermore increases PPARβ/δ levels through an unknown mechanism. Exercise-increased PPARβ/δ activity further stimulates the expression of PGC1α. By coactivating MEF2 and PPARβ/δ, PGC1α fuels a positive feed-forward signal to further increase PGC1α expression. In turn, PGC1α potentiates PPARβ/δ/RXR heterodimers that stimulate the expression of genes involved in fatty acid uptake and β-oxidation. It also stimulates the expression of nuclear respiratory factor 1 (NRF1) and NRF2, thus leading to enhanced expression of nuclear-encoded mitochondrial genes. Finally, through coactivation of MEF2, PGC1α regulates the switch to the expression of slow-twitch muscle fiber genes.

Skeletal muscles with reduced oxidative capacity, increased glycolytic capacity, and a decreased percentage of type I fibers are observed in both obese [63, 64] and diabetic patients [65]. Animals with body weight gain induced by a high-fat diet have fewer type I muscle fibers [66], as do animals with a skeletal muscle-specific deletion of PPARβ/δ. This fiber type switching in the skeletal muscles towards a lower oxidative capacity is the causative factor in the development of obesity and diabetes [43]. Along the same line of evidence, mice overexpressing the activated form of PPARβ/δ in skeletal muscles or wild-type mice administered a PPARβ/δ-specific agonist along with a high-fat diet are resistant to obesity. This finding signifies that muscle fiber conversion to type I due to activation of PPARβ/δ in these animals exerts a protective effect against obesity [42].

Enhanced PPARβ/δ-dependent muscle performance

Skeletal muscle performance is dependent on the distribution of fiber types. Exercise training increases PPARβ/δ expression and, in parallel, oxidative fibers [41]. This pattern has been confirmed in individuals showing increased PPARβ/δ levels after exercise training [67–70]. As already mentioned, the increase in the number of fibers with oxidative capability, an effect induced by muscle-specific overexpression of PPARβ/δ [41], is similar to that observed in exercised mice [71–73] and humans [74], suggesting that upregulation of PPARβ/δ plays an important role in muscle adaptation to exercise. Transgenic mice expressing constitutively active PPARβ/δ have a significantly enhanced running capacity [42]. In contrast, PPARβ/δ-null mice show reduced endurance [43]. Collectively, these observations favor a strong role for activated PPARβ/δ in the physical performance of skeletal muscles. In fact, the PPARβ/δ ligand GW501516 has been classified as a doping substance by the World Anti-Doping Agency because of its ability to influence muscle performance [75], and two of its major urinary metabolites have been characterized for identification of the drug in routine doping controls [76]. Mechanistically, PPARβ/δ can enhance running endurance through activation of AMPK signaling [77, 78] as AMPK is activated during exercise training (Figure 2) [79, 80]. Of interest, a decrease in running capacity has been observed in mice with defective AMPK signaling in muscle [81, 82]. More important, mice with an

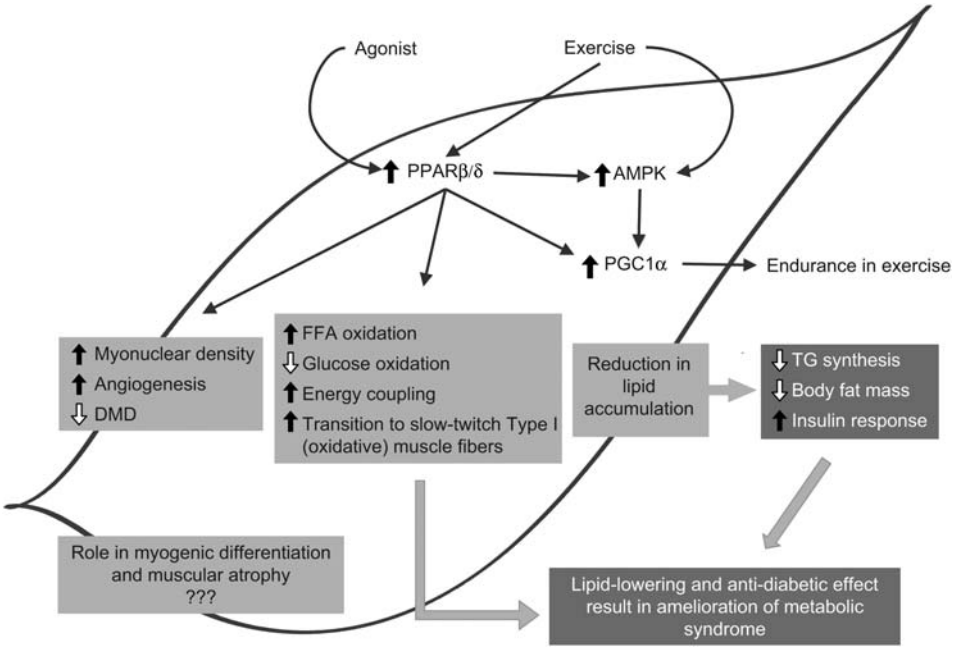

Figure 2 Actions of PPARβ/δ in skeletal muscles.
Pharmacological activation of PPARβ/δ by a specific ligand has been shown to regulate expression levels of genes involved in triglyceride hydrolysis and free fatty acid oxidation, lipid use, energy expenditure, and muscle fiber type switching in skeletal muscle, in turn resulting in decreased body fat mass and enhanced insulin response. Both the lipid lowering and the anti-diabetic effects exerted by the inducing effects of PPARβ/δ result in the amelioration of symptoms of metabolic disorders. In addition, exercise training induces fiber type switching accompanied by increased PPARβ/δ levels and AMPK, resulting in endurance in exercise through upregulation of the common effector molecule, PGC1α. Pharmacological activation of PPARβ/δ also promotes myonuclear accretion and angiogenesis in skeletal muscle and protects against Duchenne muscular dystrophy (DMD). However, the role of PPARβ/δ in myogenic differentiation and muscular atrophy remains to be deciphered. FFA, free fatty acids; TG, triglycerides.

activated form of PPARβ/δ in skeletal muscle show a constitutive high level of AMPK expression [83], and a physical association between exercise-activated AMPK and PPARβ/δ is observed, revealing a molecular link most probably contributing to the running endurance phenotype observed after activation of PPARβ/δ.

The mechanism through which PPARβ/δ is upregulated during exercise remains unclear, although one plausible explanation is that exercise results in recruitment of fatty acids that might act as endogenous ligands for PPARβ/δ, thus resulting in its activation and stimulation of its target genes (Figure 1). Another mechanism probably involves mediation through upregulation of PGC1α, as exercise training leads to increased levels of PGC1α in skeletal muscles [55, 84], which might in turn lead to increased activity of PPARβ/δ because of its interaction with PGC1α. These two possible mechanisms are, of course, not mutually exclusive.

Expert opinion

PPARβ/δ is a crucial player in regulating lipid metabolic pathways in skeletal muscle, which in turn affects other organ systems, resulting in the amelioration of metabolic disorders (Figure 2). Muscle-specific deletion of this PPAR isotype provides additional proof for its involvement in muscle physiology. In these mutated animals, a partial compensatory role of PPARα cannot be excluded because PPARα is also expressed in tissues with high rates of fatty acid oxidation, including muscle [85–87]. Furthermore, activation of PPARα induces expression of genes involved in fatty acid oxidation. A significant decrease in the expression levels of these genes has been observed in PPARα-null mice, but in tissues other than skeletal muscle [88]. Thus, the oxidative capacity of skeletal muscle appears not to be compromised in PPARα-null mice, further strengthening the importance of PPARβ/δ in metabolic regulation in this tissue. However, a recent report [89] suggests that PPARβ/δ is dispensable in skeletal muscles for regulating pathways involved in lipid metabolism. In that study, deletion of PPARβ/δ alone did not exert a significant effect on the β-oxidation pathway. Furthermore, there was apparently a lack of compensation between these two receptors, as double deletion of PPARα and PPARβ/δ resulted in a phenotype more like that of PPARα-null mice. Thus, it is currently difficult to definitively attribute exclusive roles to each of these two receptors in muscle metabolism. The reasons behind the discrepancies remain unclear. A better understanding can be obtained with muscle-specific deletion of PPARα and a combined muscle-specific deletion of both PPARα and PPARβ/δ, which remain to be performed. In animals with a germline deletion of PPARα, the muscle phenotype can, in part, result from the absence of PPARα in other tissues.

Furthermore, what has gone unexplored so far is the function of PPARβ/δ in muscle cell differentiation and thus its role in skeletal muscle disorders, such as muscle atrophy or hypertrophy. Apart from a few recent, conflicting reports [90, 91], the role of PPARβ/δ in the muscle atrophic program has not been addressed. What is known is that acute administration of a PPARβ/δ agonist activates ubiquitin proteasome proteolytic-dependent skeletal muscle atrophy [90], and although the muscle-specific E3 ubiquitin ligases MuRF1 and MAFbx are upregulated, no 20S proteasome transcriptional activity has been detected. Obviously, further studies with muscle-specific overexpression or deletion of PPARβ/δ are needed to clarify its possible role in the muscle atrophy program.

Pharmacological activation of PPARβ/δ is protective against Duchenne muscular dystrophy in *mdx* mice [91] and promotes myonuclear accretion [92]. Age-related muscle atrophy is associated with reduced numbers of oxidative myofibers, and activation of PPARβ/δ promotes fusion of muscle progenitor cells to form myofibers and increases myonuclear density. Ligand-induced activation of PPARβ/δ also promotes calcineurin-dependent fiber remodeling and angiogenesis in mouse skeletal muscle through upregulation of myogenic and angiogenic markers [59]. In spite of these interesting observations, modulation by PPARβ/δ of the different molecular pathways involved in myogenic differentiation remains to be elucidated, which might provide further insights into the roles of PPARβ/δ in muscular dystrophies.

Outlook

To counter the growing threat that the metabolic syndrome poses, one can dream of a ''magic pill'' with multifaceted effects that enable combating the various aspects of this disorder. The impact of PPARβ/δ activation on hypertriglyceridemia and insulin resistance through enhancement of fatty acid catabolism and energy expenditure in both adipose tissue and skeletal muscle confers on this nuclear receptor strong potential in the fight against obesity and diabetes. Its promising effects in different tissues make it the most favorable target for future therapeutic interventions. The potent ligand for PPARβ/δ, GW501516, which has been used in most of the preclinical studies described here, is already in clinical trials for the treatment of dyslipidemia and metabolic syndrome. Observations from Phase I clinical studies have confirmed its efficacy in altering the serum lipid profile, including increasing triglyceride clearance after a fatty meal in treated groups, thus strengthening its potential for functionality in people in addition to what has been previously observed in different animal models for dyslipidemia [93]. Furthermore, in Phase II studies, the PPARβ/δ agonist GW501516 improved multiple metabolic disorders associated with the metabolic syndrome, most probably through an increase in skeletal muscle fatty acid oxidation [94]. In that study, the PPARβ/δ agonist was more efficient than the PPARα agonist GW590735. The promise that GW501516 has shown in these clinical trials will hopefully not be undone by adverse effects that might emerge when large cohorts are treated. PPARβ/δ is involved in various tissue repair processes, such as cell survival, differentiation, proliferation, and migration. Such processes will have to be monitored carefully during long-term treatment with candidate drugs targeting PPARβ/δ.

Highlights

- Skeletal muscle is a major site of fatty acid catabolism and energy expenditure.
- PPARβ/δ is the isotype predominantly expressed in skeletal muscles and plays a pivotal role in muscular fatty acid β-oxidation.
- The role of PPARβ/δ as a central regulator of fatty acid metabolism in skeletal muscles has been established through in vitro and in vivo approaches involving transgenic animal models with either muscle-specific overexpression or deletion of PPARβ/δ.
- Pharmacological activation of PPARβ/δ by a selective ligand regulates genes involved in lipid use, triglyceride hydrolysis, fatty acid oxidation, energy expenditure, and lipid efflux in skeletal muscle.
- Agonist-induced effects of PPARβ/δ result in amelioration of obesity, insulin resistance, and glucose intolerance, revealing its potential as a therapeutic target in metabolic disorders.
- PPARβ/δ activation alters the composition of the muscle fibers towards the slow oxidative type I, in support of its protective effect against metabolic syndrome and enhancement of muscle performance during endurance exercise.
- PPARβ/δ-mediated regulation of myogenic differentiation and muscle atrophic signaling pathways remains unexplored.
- Clinical studies related to the safety and efficacy of PPARβ/δ agonists are ongoing.

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