Review article

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ROLE OF PPAR-δ IN DETERMINATION OF MUSCLE FIBER TYPE IN RESPONSE TO EXERCISE

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Endurance exercise can induce muscle fiber type change from type II glycolytic to oxidative type I muscle fibers. The exact molecular mechanism is still not clear, but the nuclear receptor PPAR-δ (peroxisome proliferator-activated receptor delta) and co-activator, perxisome-proliferator-activated receptor-gama co-activator-1α (PGC-1α) are the key factors responsible for increased mitochondrial biogenesis and increased oxidative capacity of muscle fibers, determining in this way the muscle phenotype. The paper explores the possible mechanisms of regulation and the role of PPAR-δ in the skeletal muscle and muscle fiber type determination in order to find solutions for complex physiological properties, such as fatigue and endurance. Acta Medica M*edianae 2011;50(2):57-62.*

Key words: *nuclear receptor, muscle fiber type, exercise*

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Introduction

Morphologically, histochemically and functionally, skeletal muscle fibers can be classified as: type I (slow or oxidative) and type II (glycolytic or fast) muscle fibers. There are significant differences among them in relation to the contraction, metabolism and fatigue.

Type I (slow or red muscle fibers) contains a lot of red pigment (myoglobin and mitohondrial cytochromes), so the muscles are dark red colored. They contract slower than the white fibers, but are capable of prolonged and strong contractions. These fibers mainly use oxidative metabolism for energy production and contain many mitochondria. Muscle action potential is about 100 milliseconds, which is enough for glucose and fatty acids to efficiently metabolize. Muscles are stable and long-term supply of energy from ATP, and therefore, type-I fibers are known as the "endurance muscle".

Type II (fast or white fibers) contains little less myoglobin and mitochondria, and therefore less cytoplasm. Energy for their work comes from anaerobic glycolysis. Triggering the action potential is less than 10 milliseconds and fast contractions are supported by an endoplasmic reticulum, so that they can quickly release and reabsorb by calcium ions (about ten times faster than oxidative fibers). During strong contractions they tire easily. Glycolytic metabolism leads to rapid production of lactic acid, so that the muscles need rest and recovery in order to remove lactic acid and have oxygen levels restored (1,2).

Genetic factors are often the reason for the variation in the distribution of fiber types; however, physical activity is frequently emphasized. Adult skeletal muscles are characterized by plasticity and may be subjected to conversion into different types of fibers in response to exercise or modulation of motoneural activities (3-6). A high percentage of nuclear receptor PPAR-δ in oxidative muscle fibers (10-50 times higher than the other isoforms) has pointed to its possible role in the formation of these fibers. For the regulation and activation of PPAR-δ, cofactors and ligands are required to express transcriptional activity (7-9).

Role of PPAR-δ in skeletal muscle

Skeletal muscles constitute about 50% of total body mass, so their metabolism is an important part of the overall metabolism of the whole organism. As they belong to plastic tissues, skeletal muscles adapt in response to exercise, and these local signals and molecular regulation are very important for their phenotype.

PPARs are nuclear protein receptors that act as transcription factors in the regulation of gene expression in the adipose tissue, heart, muscle, placenta, etc. This family of transcription factors in man contains 48 members, which differ structurally and functionally (10). There are three

different isoforms: α, β/δ and γ. PPAR-δ is an important metabolic sensor and regulates transcription by heterodimerizing with retinoid X receptor. The receptor complex binds to PPAR element located in the regulatory region of genes and binds to DNA in the absence of ligands. Ligand binding leads to induction of gene expression. Bonding is possible due to cavitation, and ligand specificity is determined by complementarity between the cavity and ligand (11). Ligands that activate PPAR-δ are saturated or unsaturated long chain fatty acids (12). Endogenous substances that can activate PPAR-δ, in addition to fatty acids, are triglycerides, leukotrienes, eicosanoids, prostaglandins, vitamin A metabolic retinoic acid and a large number of synthetic ligands (13,14).

Animal studies have shown that PPAR-δ plays an important role in metabolic adaptation of many tissues to changes in external conditions, and are involved in the regulation of fatty acid metabolism of the skeletal muscle and adipose tissue through the expression of genes involved in the takeover of fatty acid ß-oxidation, mitochondrial respiration, generate energy, thermo-genesis (15-18). This isoform in comparison to other PPARs is most common in the skeletal muscle (19) and has the highest expression in the oxidative type I muscle fibers compared to glycolytic type II muscle fibers (18).

It is believed that a large number of physiologic and pathologic factors affect the content of PPAR-δ in skeletal muscle. Literature data have shown that both short and endurance training increase the expression of PPAR-delta, both in human and in animal studies (20,21). Endurance training within three weeks of swimming in the animal model led to increased expression of PPARδ in the skeletal muscle, and such an increase was obtained after a single exhaustive bout of cycling in humans (22). Mazzatti et al.(23) showed that a short-term disuse of hind-limb led to increased PPAR-δ mRNA, and this marked increased expression represents an adaptive, stress-induced response in the prevention of major metabolic consequences. Thus, in patients with long-standing spinal cord injuries, the contents of this nuclear receptor decreased in the skeletal muscle (24).

Data on the impact of nutrition factors on the expression of PPAR-δ are controversial, but the general conclusion is that starvation leads to rapid but transient increase in the expression of PPAR-delta in the skeletal muscle (25,26), suggesting its important role in the metabolism of fatty acids. However, the exercise itself and muscle contractions have proved to be important regulators of the contents of the PPAR-δ in the skeletal muscle. This conclusion was induced by suppression of free fatty acids (using nicotinic acid as antilipolytic drug) with the increased mRNA expression of PPAR-δ in the skeletal muscle (27). Further research on the effects of different long chain fatty acids in cell culture showed no significant effect on the expression of PPAR-δ, what has led to the conclusion that the effect of fatty acids is an important regulator of expression. However, the nature of this regulation not been clarified yet, so that the emphasis is on the presence of activating ligands and some transporters of fatty acids (28).

Role of PPAR-δ in determination of muscle fiber type

Molecular mechanism responsible for regulating the muscle fiber type has not been defined yet. In order to prove that the PPAR-delta is responsible for the regulation and development of oxidative type I muscle fibers, a group of scientists has made transgenic mice (TG) by inserting the zygote with the viral transcription activator, VP16, combined with PPAR-δ gene (18). This has increased the transcription of PPAR-δ responsive genes and created a modified transcriptional regulation specification and growth of muscle fibers. Biopsy tissue samples were compared with normal tissues of mice and showed the increased expression of PPAR-δ protein. Mitochondrial DNA was increased more than twice in skeletal muscles and muscle fibers possessed the markers of oxidative muscle. The whole physiology of the physical abilities of the mutant mouse was much more advanced than the normal type of mice, including the postponement of fatigue and better physical performances. These progressive changes in oxidative capacity and, consequently, the changes in the type of muscle fibers, led to a significant improvement in the profile of exercise, not just a result of higher expression of PPAR-δ. In a recent report by Luquet et al. (29), a simple activation of PPAR-δ expression in muscle was not enough to change the type of fiber, although the oxidative enzymes were increased. This fact proves that both activation signals and ligands are necessary and important. Possible regulatory role of PPAR-δ in determining the type of muscle fiber is perhaps the increased expression of his coactivators or reduction of his corepressors (30). Increased expression of PPAR-δ has also lead to increased expression of genes involved in fatty acid catabolism. All these results obtained in experiments with transgenic animals are the result of altered expression of mRNA during active muscle development. Whether these processes are present in the regulation of muscle fiber types in adult and mature muscle as well is not entirely clear. Such data related to humans are very scarce (31,32), which points to the necessary caution in comparing data in animals and man. However, even in the skeletal muscle in humans, a higher expression of PPAR-δ and PGC1-α has been recorded in individuals with greater portion of muscle fiber type I (for

example, in elite cyclists) as well as their significantly reduced expression in people with spinal cord injuries, in which type I fibers have been selectively lost (23). With the change of muscle fiber types, PPAR-δ also leads to increased muscle vascularization (33-35).

These experiments favor the hypothesis that PPAR-δ plays an important role in the adaptive response of skeletal muscle to endurance exercise. Increased expression of PPAR-δ was observed after several weeks of exercise in the animal model, and similar changes were found in human muscle (26). What the molecular mechanisms that lead to increased expression of PPAR-δ in skeletal muscle during endurance training are remains unclear. Also, the relationship between the levels of expression and activation PPAR-δ and the proliferation of myoblasts and formation of certain types of muscle fiberson is not quite clear. Possible responses include the creations or increasing of ligand number for PPAR-δ under the influence of exercise, where the burning of fatty acids in the tissues, together with their metabolites, can affect the activation of PPAR-δ. According to another model, exercise can induce the expression of PGC-1α (gamma co-activator 1alfa), which then activates PPAR-δ (which is otherwise happening in the experiments, even in the absence of ligand) (36-38). This coactivator is present in tissues with higher metabolic activity, liver, brain, heart, adipose tissue and skeletal muscle (39,40) which are characterized by a large number of mitochondria, because of high energy demands. It has been noted that muscles during exercise increase mitochondrial content, enhance the expression of mitochondrial genes (cytochrome oxidase) and myoglobin and are resistant to fatigue (41), demonstrating the important role of PGC-1α for the metabolic changes in the muscle (42). Its experimentally increased expression also showed a protective effect of the changes associated with atrophy (43). Mechanisms by which PGC-1α induced changes in the muscle appeared to involve calcium calmodulin-dependent protein kinase (44), activation of calcineurin and activation of transcription factors (45,46). The ctivation of this signaling pathway leads to increased transcription of genes expressed in oxidative fibers and results in enhanced mitochondrial biogenesis (47-49). A detailed study of Lin et al. on the animal model (8) marks this coactivator as an important physiological regulator for type-I fibre specification, but also points to the fact that PGC-1 α does not completely convert all the fibers, including thus other signals which can determine a muscle fibre phenotype.

Muscle remodeling that occurs by the activation of this nuclear receptor may be associated also with endocrine function of the skeletal muscle. Physical exercise that increases the burning of fatty acids, also changes the level of muscle cytokine secretion, which are denoted as myokines in controlling metabolic responses of other tissues, especially adipose tissue (50). Important metabolic link between the skeletal muscle and adipose tissue is reflected in the total body mass, insulin sensitivity and metabolism of fatty acids. This link is not a unidirectional flow of messengers from the "endocrine" adipose tissue to a rather "passive" muscle (as previously explained their relationship); moreover, these skeletal muscles are considered another endocrine tissue able to express a large number of molecules with endocrine actions. Right here is the place PPAR-δ, which connects the functions of these tissues and in some, yet unexplained manner, maintains the metabolic balance (51). The correlation between interleukin IL-6 and PPAR-δ is also interesting, because exercise induces both an increase in PPAR-δ expression and increase in IL-6 release (52). The interleukin-6 favors fatty acid oxidation in skeletal muscle during exercise, so there is a hypothesis (53) about a role of IL-6 during endurance exercise in changing muscle fiber composition towards a more oxidative, more insulin-sensitive muscle fiber, although the molecular basis is unclear.

Conclusion

There is strong evidence that PPAR-δ is one of the key regulators in determining the type-I oxidative muscle fibers in skeletal muscles, which are determinants of endurance and speed, although the exact molecular mechanism is still unknown. Possible mechanisms include exercise-induced burning of fatty acids, or induce coactivator PGC-1-α, which both increase the expression of PPAR-δ, and activates the mitochondrial biogenesis and oxidative metabolism, which affects the phenotype of the muscle fibers. The fact that various pharmacological activators and ligands may induce the increased expression of PPAR-δ and enhance physical performance raises numerous questions about the manipulation and solutions for complex physiological abilities, such as fatigue and endurance. A promising concept of such drugs requires further studies into molecular regulatory role of PPARδ in the human muscle physiology to ensure their effective and safe use.

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ULOGA PPAR-δ U DETERMINACIJI MIŠIĆNIH VLAKANA U ODGOVORU NA VEŽBANJE

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Naporno vežbanje može indukovati promenu tipa mišićnog vlakna od tipa II glikolitičkog ka tipu I oksidativnom mišićnom vlaknu. Tačan molekularni mehanizam još uvek nije jasan, ali nuklearni receptor PPAR-δ (peroxisome proliferator-activated receptor delta) i koaktivator PGC-1-α (peroxisome proliferator-activated receptor-gama co-activator-1α) ključni su faktori koji su odgovorni za povećanu mitohondrijalnu biogenezu i povećanje oksidativnog kapaciteta mišićnog vlakna, određujući na taj način fenotip mišića. Rad istražuje moguće mehanizme regulacije i uloge PPAR-delta u skeletnim mišićima i determinaciji tipa mišićnog vlakna u cilju pronalaženja rešenja za kompleksne fiziološke sposobnosti kao što su zamor i izdržljivost.. *Acta Medica Medianae 2011;50(2):57-62.*

***Ključne reči**: nuklearni receptor, tip mišićnog vlakna, vežbanje*