REVISTA MEXICANA DE ENDOCRINOLOGÍA, METABOLISMO & NUTRICIÓN REVIEW ARTICLE

Molecular basis of exercise

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ABSTRACT

After practicing exercise you can see that the body gets some changes, and depending the kind of exercise, you will obtain different results. Researchers have investigated the relevance of performing resistance training and endurance training on muscle gain and improvement of aerobic capacity. Actually, it is well known that depending of the kind of exercise, there are differences in the gene expression, and therefore while some pathways are activated, others are deactivated. Exercise performance leads to the activation of different molecular pathways that are responsible for the increase of mitochondrial biogenesis, synthesis of both protein and muscular, and the activation of genes related with electron transport chain, depending on whether the exercise is endurance or resistance training. Some studies have shown that endurance training causes mitochondrial biogenesis through the activation of some proteins like peroxisome proliferator-activated receptor gamma co-activator 1 alpha, adenosine monophosphate-activated protein kinase, p38, nicotinamide adenine-dependent protein deacetylase sirtuin, and CAT. On the other hand,

RESUMEN

Después de la práctica continua de ejercicio se puede observar que el cuerpo va sufriendo algunas modificaciones, las cuales pueden variar dependiendo del tipo de ejercicio. La investigación de la relevancia tanto del ejercicio aeróbico como el ejercicio de fuerza sobre la ganancia muscular y la mejoría en la capacidad aeróbica ha comenzado a ser mayor. Actualmente se sabe que dependiendo del tipo de ejercicio hay diferencias en la expresión génica y por lo tanto en vías de señalización, donde se ha visto que mientras unas vías se activan otras son desactivadas. Algunos estudios han mostrado que el ejercicio aeróbico provoca biogénesis mitocondrial a través de la activación de algunas proteínas tales como PGC-1α, AMPK, p38, SIRT y carnitina aciltransferasa (CAT); por otro lado, el ejercicio de fuerza conduce a la activación de genes involucrados en biogénesis muscular y proteica a través de proteínas como PDK, mTOR, ERK, p70S6K1, entre otras. Recientemente se ha demostrado que la combinación de ambas clases de entrenamientos incrementa la activación de proteínas involucradas en ambas

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resistance training leads to the activation of genes involved in both muscular and protean biogenesis throughout some proteins like phosphoinositide-dependent protein kinase, mammalian target of rapamycin, extracellular signal-regulated kinase, and p70S6K1. Recently, it has been shown that a combination of both kinds of training increase the activation of protein involved in both molecular pathways in comparison with the practicing of resistance training. Therefore, it is recommended to perform both types of exercises if the person wants to obtain mitochondrial and muscular gain. (REV MEX ENDOCRINOL METAB NUTR. 2015;2:185-93)

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rutas moleculares en comparación con la práctica de entrenamiento de fuerza. Por lo tanto, es recomendado realizar ambos tipos de ejercicios si la persona quiere obtener ganancia muscular y mitocondrial.

Palabras clave: Ejercicio. mTOR. AMPK. PGC-1α.

INTRODUCTION

Recently in Mexico, the number of people who exercise have decreased. Data from ENSANUT 2012 (Encuesta Nacional de Salud y Nutricion) show that the prevalence of physical inactivity increased significantly by 47.3% in comparison with ENSANUT 2006[1].

The importance of a healthy diet and exercise are linked with genetic profile. Both diet and exercise have an influence on genetic expression, known as epigenetic changes[2]. Epigenetics can be defined as somatically heritable states of gene expression resulting from changes in chromatin structure without alterations in the DNA sequence, including DNA methylation, histone modifications, and chromatin remodeling[3].

Therefore, is important to understand the changes in DNA expression due to transition from sedentary to exerciser. This review focuses on the pathways and modification in molecular expression caused by exercise (endurance or resistance training) in order to understand why and how these differences take place.

PHYSICAL ACTIVITY, EXERCISE AND SPORT

There are differences between physical activity, exercise, and sport that are necessary to define before introducing the issue of the molecular basis of exercise.

Physical activity involves corporal movements caused by muscular contraction resulting in energy consumption, and can be divided into structured and non-structured. Non-structured physical activity involves daily movements as walking, sweeping, mopping, and driving[2,4]. Structured physical activity includes exercise and sport.

Exercise is a voluntary act and accepted with the objective of improving or maintaining good health[2].

Sport is a physical activity that, unlike exercise, is institutionalized and regulated, developed in competitions that have as an aim to obtain the maximum performance of the athlete[2,5,6].

Independently of exercise or sport, there are several genes that encode for proteins expressed during this events. Some of these proteins act by activating or inhibiting mitochondrial biogenesis and synthesis of muscle. Table 1 shows the proteins that play a role in these events.

MITOGEN-ACTIVATED PROTEIN KINASE AND EXERCISE

Mitogen-activated protein kinase (MAPK) is a family of serine-threonine kinase mediators of

Table 1. Protein involved in mitochondrial and muscular biogenesis

Mitochondrial biogenesis	
Protein	**Function**
PGC-1α	Activates transcriptional factors involved in mitochondrial biogenesis
CaMK II	Activates p53, PGC-1α, NRF1 and NRF2
p38MAPK	Involved in activation of p53, PGC-1α, NRF1 and NRF2
AMPK	Involved in activation of p53, PGC-1α, NRF1 and NRF2
p53	In nucleus, induces expression of Tfam, PGC-1α, Drp1, Mfn2, SCO2, AIF, and HSP70. In mitochondria coordinates expression of COX subunits
HSP70	Acts as chaperone molecule in mitochondria biogenesis
AIF	Is necessary for correct assembly of complex 1 in respiratory chain
COX	Protein involved in electron transport chain
SIRT1	Activates PGC-1α throughout deacetylation
GCN5	Activates PGC-1α throughout deacetylation
Muscular biogenesis	
p70S6K	Activates eIF4B, eIF4A, eEF2, and pS6
eEF2	Activates protein elongation in translation
rpS6	Involved in translation as part of ribosomal 40S subunit
Myostatin	Inhibits muscular hypertrophy
mTOR	Activates p70S6K and 4E-BP
ERK1/2	Phosphorylates TSC2
PDK	Activates Akt
4E-BP1	Acts in the initiation of translation
Akt/PKB	Activates mTOR and dissociates complex TSC1/TSC2 throughout phosphorylation of TSC2

p70S6K: 70 kDa ribosomal protein S6 kinase; eEF2: eukaryotic elongation factor-2; rpS6: ribosomal protein S6; mTOR: mammalian target of rapamycin; ERK1/2: extracellular signal-regulated kinase; Akt (PKB), PDK: 3-phosphoinositide-dependent protein kinase; 4E-BP: 4E-binding protein; PGC-1α: peroxisome proliferator-activated receptor and co-activator; CaMK II: calcium/calmodulin-dependent protein kinase II; p38MAPK: p38 mitogen-activated protein kinase; AMPK: AMP-dependent protein kinase; HSP70: heat shock protein 70; AIF: apoptosis-inducing factor; COX: cytochrome oxidase: SIRT1: NAD-dependent deacetylase sirtuin-1; GCN5 acetyltransferase GCN5.

intracellular signaling pathways associated with a variety of cellular activities that include cellular proliferation, differentiation, transformation, and cellular death[7,8,] . The MAPK family in humans consist in extracellular signal-regulated kinase 1 and 2 (ERK1/2), p38, c-Jun N-terminal kinase (JNK) and ERK5[9]. The MAPK is stimulated by cytokines, growth factors and cellular stress, which is reflected in the increase of lipopolysaccharides, reactive oxygen species (ROS), Ca^{2+}, and endoplasmic reticulum stress[8].

Exercise is considered as one of the metabolic process that generates major stress, and is an activator of ERK1/2, JNK, and p38. Each MAPK has different targets. The p38 activates p53 throughout phosphorylation of serine[10]. With this activation, p53 translocates to the mitochondria where it increases expression of mitochondrial-encoded subunits of the COX complex. In addition, p53 translocates to the nucleus where it induces expression of Tfam, Drp1, Mfn, SCO2, AIF, HSP70 and PGC-1α[11], increasing vascular endothelial growth factor (VEGF), proliferator of peroxisome-activated receptor (PPAR) and mitochondrial biogenesis[12]. When ERK is activated, this and its RSK substrate phosphorylates to TSC2 with a subsequent inhibition of complex TSC2/TSC1 and the activation of mTOR through of Rheb[13-16]. The ERK phosphorylates to raptor, inducing the activation of mTORC1[16,17]. The activation of different MAPK members during exercise is dependent on the type,

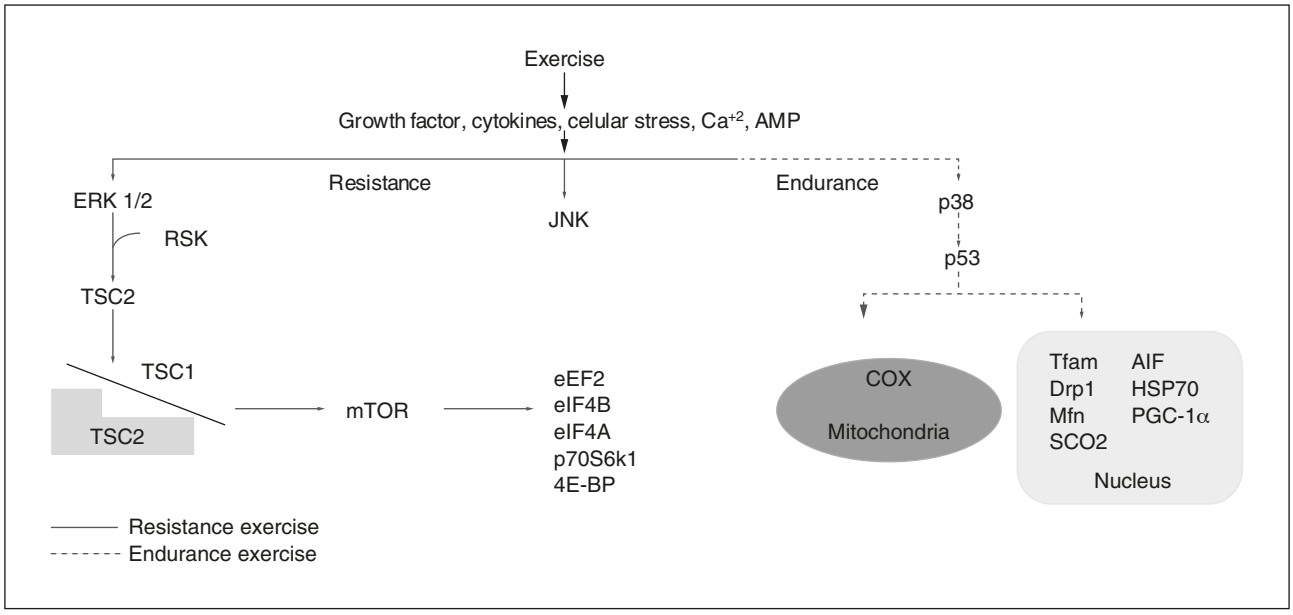

Figure 1. Activation of different mitogen-activated protein kinase by exercise. ERK 1/2: extracellular signal-regulated kinase; JNK: c-Jun N-terminal kinase; TSC1: tuberous sclerosis complex 1; TSC2: tuberous sclerosis complex 2; mTOR: mammalian target of rapamycin; eEF2: eukaryotic elongation factor; eIF4A: eukaryotic initiation factor 4A; eIF4B: eukaryotic initiation factor 4B.

duration, and intensity of contractile stimulus. Therefore, MAPK can be activated by endurance or resistance training. Endurance training activates p38[18-20], while resistance training increases phosphorylation and therefore activity of ERK1/2[21-23], leading to activation of metabolic pathway related with mitochondrial and muscular biogenesis, respectively (Fig. 1).

ADENOSINE MONOPHOSPHATE-ACTIVATED PROTEIN KINASE AND EXERCISE

Adenosine monophosphate-activated protein kinase (AMPK) is a heterotrimer enzyme composed of a catalytic-α subunit and regulator-β and γ subunits. This enzyme is considered as a fuel detector, which is present in mammalians[24]. The AMPK is activated by the increase of cellular concentration of adenosine monophosphate (AMP) and the decrease of adenosine triphosphate (ATP) due to the increase of energy expenditure or a limited synthesis of ATP[25]. When there is an AMP increment due to exercise, AMPK activation inhibits its ATP-consuming pathways and activates fatty acid and carbohydrate metabolism to restore ATP levels in muscle. Exercise, considered as one of the metabolic processes that generates metabolic stress, is perhaps one of the principal activators of the increase in the AMP:ATP ratio[25,26]. With exercise performance, the energetic necessities increase, and this in turn induces a decrease of the ATP levels, leading to an increase of AMP levels. During muscular contraction, although ADP is the result of the breakdown of ATP, adenylate kinase transforms ADP to AMP. The AMPK is also activated by the adipocytokines leptin and adiponectin[27]. There is evidence that the reducing of glycogen due physical activity is responsible for activating AMPK[28]. The direct antagonist of AMPK activity is ATP. Activation of AMPK inhibits protein synthesis through inhibition of mammalian target of rapamycin (mTOR) and activation of kinase of eEF2, which provokes an increase in eEF2

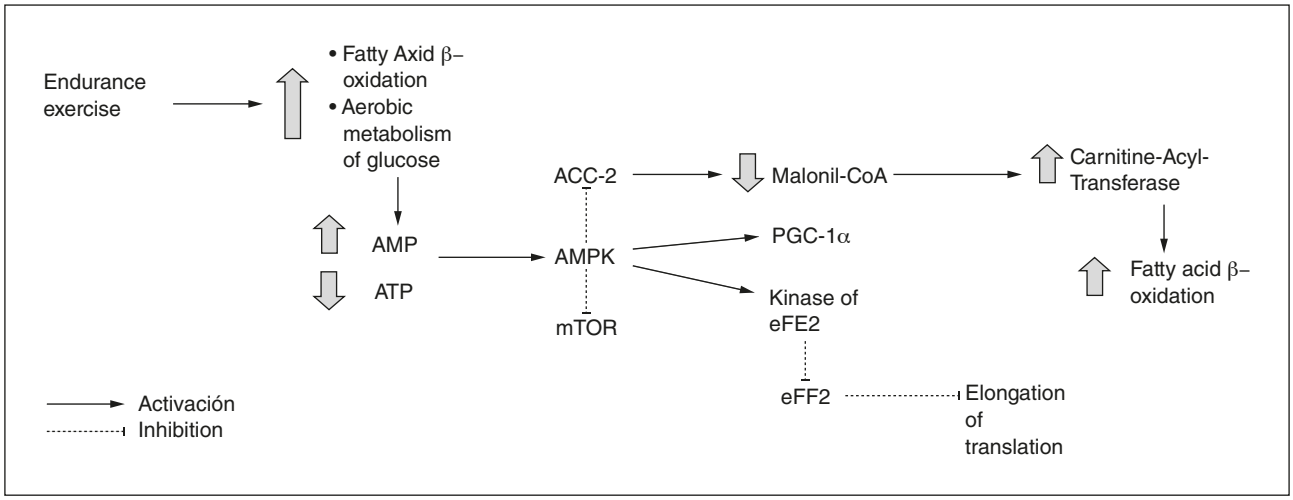

Figure 2. Activation of adenosine monophosphate-activated protein kinase throughout exercise. AMP: adenosine monophosphate; ATP: adenosine triphosphate; AMPK: adenosine monophosphate-activated protein kinase; mTOR: mammalian target of rapamycin; ACC-2: acetyl-CoA-carboxylase 2; PGC-1α: peroxisome proliferator-activated receptor gamma co-activator 1 alpha; eEF2: eukaryotic elongation factor 2.

phosphorylation and inhibition of protein elongation[29]. The activation of AMPK increases the oxidation of fatty acids by phosphorylation of acetyl-CoA-carboxylase (ACC-2), diminishing levels of malonyl-CoA, an inhibitor of carnitine-palmitoyl transferase-1. Another result due to activation of AMPK is the activation of PGC-1α, a regulator of mitochondrial biogenesis (Fig. 2). Evidence shows that endurance exercise (60-80% VO_{2max}) increases AMPK activity[21,30-34], although it has been reported that after a period of continued exercise, AMPK levels decrease compared to levels prior to exercise[35].

PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR AND CO-ACTIVATOR ALPHA AND EXERCISE

Peroxisome proliferator-activated receptor and co-activator alpha (PGC-1α) is a member of a transcriptional co-activator family named PGC[12]. It is proposed that PGC-1α is the main regulator of mitochondrial content because it is a key activator of genes involved in mitochondrial biogenesis[36]. Several types of PGC-1α have been discovered, such as PGC-1α-a, PGC-1α-b, PGC-1α-c, and N-Truncate-PGC-1α (NT- PGC-1α)[37] that is the result of alternative splicing. Exercise leads to a consumption of ATP with an increase of AMP and therefore the activation of both p38 MAPK and AMPK[38], causing the phosphorylation of PGC-1α at Thr177 and Ser538 sites[27]. The diminishing of NADH/NAD ratio caused by exercise activates Sirtuin-1; this is a protein with deacetylase activity, leading to PGC-1α deacetylation[30]. It has been shown that an alternative pathway for PGC-1α deacetylation is through GCN5 acetyltransferase. After a bout of exercise, GNC5 levels decrease, causing a diminishing of PGC-1α acetylation[31]. Both phosphorylation and deacetylation of PGC-1α increase its activity[30], producing the translocation of PGC-1α to the nucleus where it activates the nuclear respiratory factor-1 and 2 (NRF-1 and NRF-2). These factors bind to the cytochrome C subunit and to promoter of cytochrome oxidase subunit, respectively[18]. Activation of this signaling pathway leads to mitochondrial biogenesis and

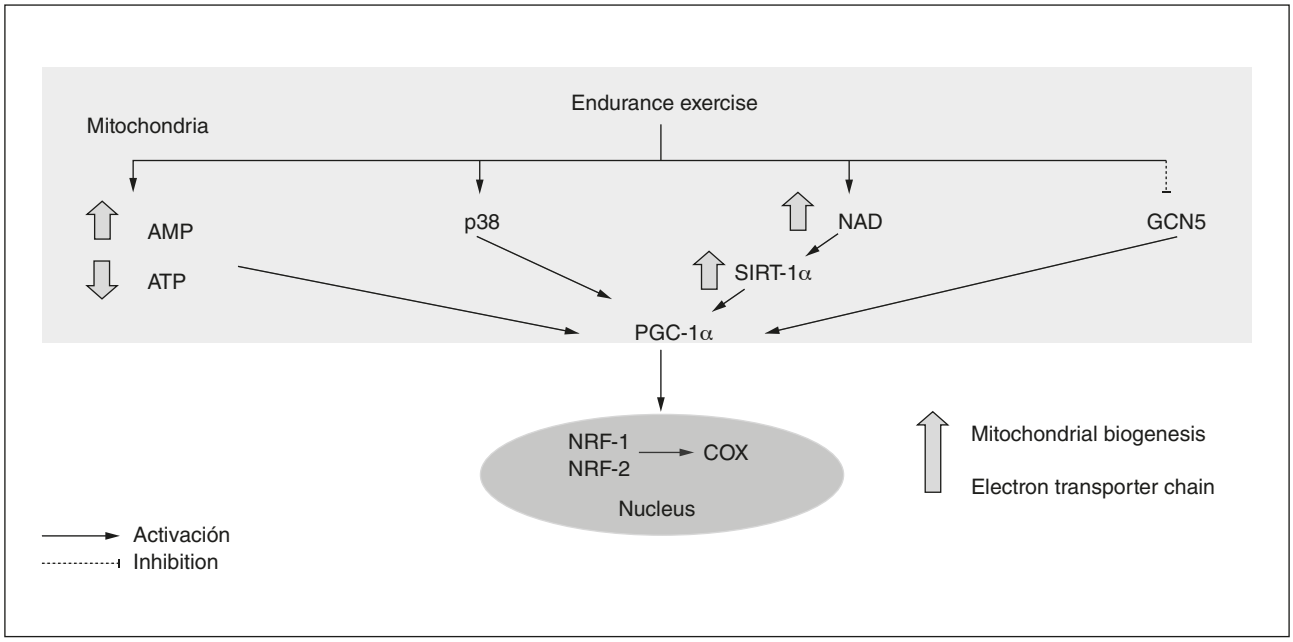

Figure 3. Activation of peroxisome proliferator-activated receptor gamma co-activator 1 alpha by exercise. AMP: adenosine monophosphate; ATP: adenosine triphosphate; NAD; nicotinamide adenine dinucleotide; SIRT1: NAD-dependent protein deacetylase sirtuin-1; GCN5: acetyltransferase GCN5; PGC-1α: peroxisome proliferator-activated receptor gamma co-activator 1 alpha; NRF-1: nuclear respiratory factor 1; NRF-2: nuclear respiratory factor 2; COX: cytochrome oxidase.

the increase of electron transport chain, helping to prolong the time in which energy comes from aerobic metabolism (Fig. 3). Expression of NT-PGC-1α activates the expression of VEGF and PPARs; these molecules induce angiogenesis and an increase of fatty acid oxidation. PGC-1α is activated by both endurance exercise and the combination of endurance followed by resistance exercise after a period of rest[36]. Some authors have reported that levels of PGC-1α decreased during chronic exercise in comparison with a single bout of exercise, and therefore changes in exercise training is recommended in order to avoid physiological adaptation[39].

MAMMALIAN TARGET OF RAPAMYCIN AND EXERCISE

The mammalian target of rapamycin is a Ser/Thr kinase protein member of phosphoinositol-3-kinase-related kinases (PIKKs) that are involved in the increase of protein synthesis and muscle by the regulation of initiation and elongation factors and ribosomal biogenesis[40]. Nowadays, it is known that mTOR binds to both raptor and rictor to form two different complexes, both in function and structure; these complexes are mTORC1 and mTORC2 respectively[41]. The mTORC1 inhibits the insulin signal through its downstream substrate S6K1, followed by the inhibition of the phosphorylation of insulin receptor substrate 1 (IRS1). On the other hand, mTORC2 regulates positively the insulin translation signal by the phosphorylation of PKB/Akt on the Ser473 site[40,41]. When PKB/Akt is phosphorylated, this is responsible for activating mTOR[42], which is inhibited through AMPK[43]. The activation of mTOR leads to either the phosphorylation and activation of some proteins involved in the initiation and elongation of the translation and in the muscular protein synthesis in humans[44], such as eIF4E-binding protein-1 (4E-BP1) and p70S6 kinase1 (p70S6K1)[45], or dephosphorylation of eukaryotic elongation factor 2 (eEF2)[21,44] (Fig. 4). Although the results obtained by several

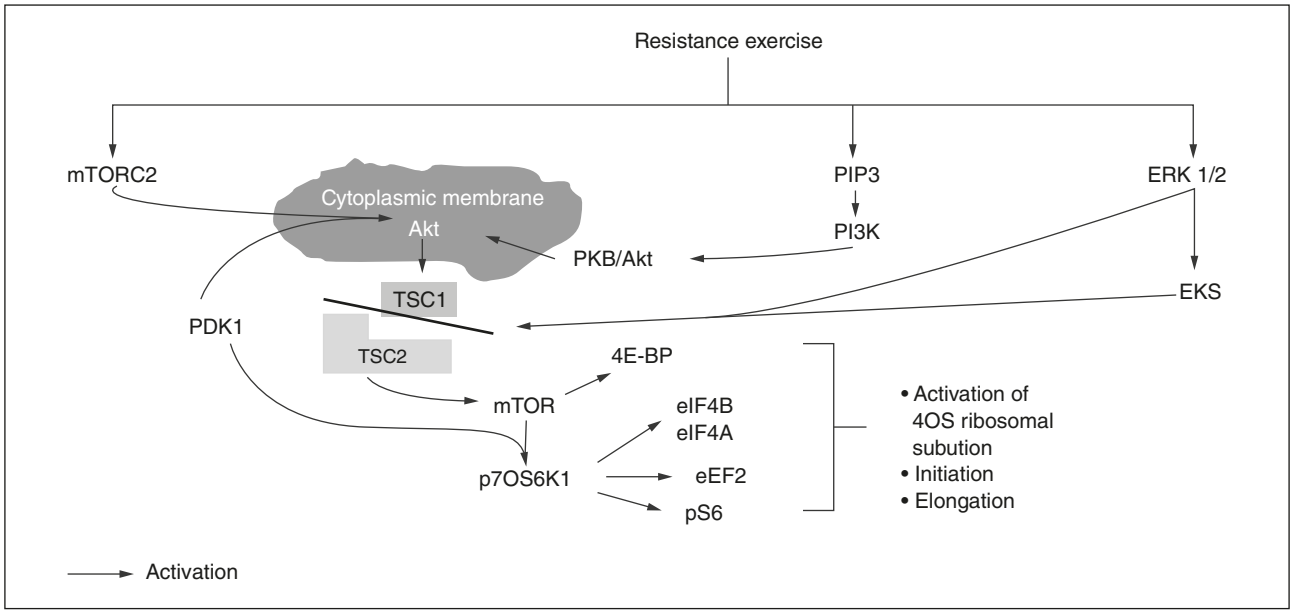

Figure 4. Signaling pathway throughout exercise. mTOR2: mammalian target of rapamycin complex 2; PI3K: phosphoinositide 3 kinase; ERK1/2: extracellular signal-regulated kinase; Akt: protein kinase B; PIP3: phosphoinositide-3,4,5-triphosphate; PDK1: phosphoinositide-dependent kinase; TSC1: tuberous sclerosis complex 1; TSC2: tuberous sclerosis complex 2; AMPK: adenosine monophosphate-activated protein kinase; 4E-BP: 4E-binding protein; p70S6K1: p70S6 kinase 1; eEF2: eukaryotic elongation factor 2; eIF4A: eukaryotic initiation factor 4A; eIF4B: eukaryotic initiation factor 4B.

researches on resistance exercise show an increase in the phosphorylation of mTOR, a study shows that a combination of endurance training with resistance training increases the activity of targets where mTOR acts, although this increase is not significant. None of these studies reference any complex of mTOR.

RIBOSOMAL PROTEIN S6 KINASE 70-KDA AND EXERCISE

Ribosomal protein S6 kinase 70-kDa (p70S6K) is encoded by *ps6kb1* gene, a member of the cyclic AMPK[48]. The p70S6K is a Ser/Thr kinase regulated by both phosphoinositide-3-kinase (PI3K)/mTOR and Ras/MAPK[14]. Both IRS and growth factor receptors activate PI3K either directly or indirectly, respectively. Activation of PI3K produces the formation of phosphoinositide-3,4,5-triphosphate (PIP3), causing Akt to translocate into the plasmatic membrane where is activated by mTORC2 and 3-phosphoinositide-dependent protein kinase (PDK). When Akt is activated, this phosphorylates to tuberose sclerosis complex 2 (TSC2) in Ser939 and Thr1462 sites, causing an inhibition on inhibitory effect of the TSC1/TSC2 complex on mTORC1. Once mTORC1 is activated, this along with PDK is responsible for phosphorylation of p70S6K on Thr421/Ser424 and Thr229 sites, respectively. Ras/MAPK is another way in which mTORC1 is activated; in this pathway ERK and its substrate ESK phosphorylate to TSC2, causing the same effects as mTORC1 and PDK on TSC1/TSC2 complex. When p70S6K is activated, this activates to S6 ribosomal protein, component of 40S ribosomal subunit, which regulates the initiation and elongation of translation through phosphorylation of eukaryotic initiation factor 4A (eIF4A) and eukaryotic initiation factor 4B (eIF4B) (Fig. 4)[49,50]. There is evidence that resistance training increases the activity of p70S6K both in men and women[43-47]. On the other hand, Lundberg, et al. found that a combination of endurance with resistance training increases the p70S6K activity in comparison with resistance training[36].

CONCLUSION

Exercise performance leads to the activation of different molecular pathways, which are responsible for the increase of mitochondrial biogenesis, synthesis of both protein and muscular, and the activation of genes related with electron transport chain, depending on whether the exercise is endurance or resistance training. Recently, evidence shows that a combination of both kinds of training increases the activation of protein involved in both molecular pathways in comparison with the practicing of resistance training. Different studies demonstrate that continuous repetition of the same either resistance or endurance training leads to diminishing of the content and activation of signaling pathways, either mitochondrial or protein synthesis, and it is recommended to change the kind of training constantly in order to avoid adaptation. Therefore, the combination of endurance and resistance training is recommended.

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