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Curcumin Potentially to Increase Athlete Performance Through Regulated Mitochondrial Biogenesis

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Abstract. A marked example of muscle adaptations occurs in the mitochondria following exercise training. Endurance training has potential to enhance metabolic characteristics in the skeletal muscle, including mitochondrial biogenesis and glucose transporter 4 (GLUT4). Polyphenol have been shown to activate cAMP, therefore, currently being intensively investigated as potential inducer of mitochondrial biogenesis through the deacetylation-mediated activation of PGC-1α. The polyphenol curcumin is components of curcuma longa L, have ability to regulated mitochondria biogenesis on skeletal muscle will review in this chapter. The examination the effect of combination of endurance training and curcumin treatment to increase mitochondrial biogenesis seem look like through AMPK, SIRT1 and PGC-1α pathway. Furthermore, in this review we also explained the direct target how curcumin treatment increase mitochondrial biogenesis. We focus on the second messenger cAMP which involve to regulated mitochondrial biogenesis. Indeed, previous study indicated that cAMP be the important target on endurance exercise training to increase mitochondrial biogenesis. The last, the current review determined how curcumin have ability to increase mitochondrial biogenesis on skeletal muscle with examine phosphorylation of PDE4A which involve to convert cAMP to AMP. Based on our previous experiments we conclude that indeed curcumin treatment have ability to increase performance through regulated mitochondria biogenesis on skeletal muscle.

1. Introduction

The skeletal muscle is one of the largest organs in the body, and it has great adaptive potential in response to physiological stressors. A marked example of muscle adaptation occurs in the mitochondria following exercise training. The biogenesis of mitochondria and the clearance of damaged mitochondria can promote healthy muscle. This conditions have ability to protect metabolism from imbalance. Previous research for several decades have indicated that adaptations have been happen on this situation, unfortunately their underlying mechanisms remain to be elucidated. Many experiments showed that Peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α) has been implicated as a master regulator of mitochondrial biogenesis. Furthermore, PGC-1α will interact with nuclear respiratory factor 1 (NRF1) and nuclear respiratory factor 2 (NRF-2/GA-binding protein-A) activating the mitochondrial transcription factor A (Tfam), which is responsible for transcribing nuclear-encoded

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mitochondrial genes, as well as the transcription, translation, and repair of proteins involved in mitochondrial DNA (mtDNA) [1,2]. On the other way, the expression levels of PGC-1α, (both mRNA and protein) increase following acute endurance exercise [3,4,5,6] and endurance exercise training [7,8], thus suggesting that PGC-1α is a potential regulator of metabolic adaptations after endurance exercise. PGC-1α and NRF-1 activate mitochondrial transcription factor A (TFAM) that is responsible for transcribing nuclear encoded mitochondrial proteins, including structural proteins as well as proteins involved in mitochondrial DNA (mtDNA) transcription, translation, and repair [1,2].

2. Curcumin Increase Mitochondrial Biogenesis through AMPK-SIRT1-PGC-1α mediated pathway

Our previous study examined the effect of curcumin treatment itself and curcumin together with endurance training to identify their effects on the mitochondrial biogenesis in rats skeletal muscle [9]. In that study, we showed that eTR increased phosphorylation the AMP-activated protein kinase (AMPK) on skeletal muscle and curcumin treatment have ability augment effect of eTR. Eendurance exercise training induces skeletal muscle mitochondrial biogenesis and improves performance by increasing oxidative capacity [10,11]. AMPK is the enzyme which have ability to serve as a metabolic sensor. AMPK is activated directly by elevations of [AMP] / [ATP] ratio in cells [12,13]. Furthermore, AMPK inhibits biosynthetic pathways, thus conserving energy while it activates catabolic pathways, thereby generating more ATP. Previous study had showed evidence that curcumin treatment has ability to increase phosphorylation AMPK in skeletal muscle and improves insulin resistance [14]**.** One previous study also strengthened this statement with their result which showed that curcumin increased the phosphorylation of AMPK in fat tissue of high fat diet fed C57/BL mice [15], this conditions indicates that AMPK pathway might be a target for curcumin in regulating mitochondria biogenesis on skeletal muscle. Collectively, these results suggest that curcumin treatment together with eTR can enhance phosphorylation AMPK on skeletal muscle.

In our animal's experiments, especially on gastrocnemius, we determine that curcumin itself and together with eTR increase SIRT1 protein expression and NAD^+/NADH ratio. The mechanisms underlying the increase of SIRT1 protein content with endurance training are unclear at present. One potential candidate is nitric oxide synthase (NOS). Another candidate is AMPK, endurance exercise increases AMPK activity in skeletal muscle [16,17]. It is therefore plausible that AMPK mediates the endurance exercise induced SIRT1 protein expression in skeletal muscle. The level of expression and phosphorylation of endothelial NOS is associated with SIRT1 expression in endothelial cells [18] and [19]. This is clearly that increasing SIRT1 protein expression with endurance exercise is mediated by a dynamic interaction between these two pathways NOS and AMPK has been shown to activate SIRT1, likely through an indirect increase in cellular NAD^+ levels [20].

Consistent with the above result, our result indicated curcumin treatment augment the eTR effect to decreased acetylation PGC-1α on skeletal muscle. Within skeletal muscle, SIRT1-mediated peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) deacetylation is potentially key for activating mitochondrial biogenesis. SIRT1 appears to contribute in the chronic regulation of metabolism through a pathway in which it deacetylates and activates peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) [21]. PGC-1α is a coactivator involved in activating both nuclear and mitochondrial transcription, resulting in mitochondrial biogenesis and upregulation of genes involved in lipid metabolism and oxidative phosphorylation [22,23,24]. This result shown that curcumin treatment has ability to improve PGC-1α which had known be master regulator of mitochondria biogenesis.

3. Inhibition of cAMP synthesis abolish the impact of curcumin administration in rodent skeletal muscle

The cAMP/PKA pathway is an intracellular signalling system involved in regulating many of the functions of eukaryotic cells [25]. When a G-protein–coupled receptor on the surface of a cell binds to its particular ligand, the receptor may stimulate the intracellular production of cAMP by the adenylyl cyclase associated with that receptor [25]. cAMP can then diffuse through the cytoplasm, where it interacts with various targets. Thus, cAMP serves as a second messenger within a cell. Our previous result indicated that curcumin increase cAMP level in gast [9]. Whether, inhibition of Phosphodiesterase (PDE) by PDE inhibitor rolipram also increase cAMP [26]. This evidence indicated that magnitude cAMP level due of both factors. On the other side, the other polyphenol (Resveratrol) increases cAMP levels, not by increasing cAMP production, but by inhibiting cAMP PDEs, which hydrolyze cAMP to AMP [27]. This evidence seems look like that polyphenol more prefer to inhibit PDE to increase cAMP. Furthermore, we also interested to examine effect of curcumin treatment combined with exercise. As predicted, our result showed that curcumin ability to additive exercise effect to increase cAMP level on skeletal muscle. Exercise increases the levels of glucagon and catecholamine's, which bind to their receptors and increase cAMP production by activating adenylate cyclase [27]. Based on this evidence we speculated that magnitude of cAMP level on curcumin treatment together with exercise due parallel effect through increasing adenyl cyclase and inhibition of PDE.

The most common downstream effectors of cAMP is Protein Kinase A (PKA) [25]. When a molecule of PKA binds to four molecules of cAMP, the PKA molecule releases two subunits to induces enzyme activity on target proteins [28] included phosphorylation of LKB-1 and CREB. Indeed, our result indicated that curcumin have ability to increase phosphorylation LKB-1 and CREB in Gas and when combined with exercise curcumin additive exercise effect increased phosphorylation of LKB-1 and CREB. LKB-1 is the upstream target from AMPK which can act as an energy sensor of the cell and works as a key regulator of mitochondrial biogenesis. However, it has been reported that PKA involved to increased phosphorylation of LKB-1 [29]. Since PKA activity dependent of cAMP, we suggested that cAMP participated to induced phosphorylation of LKB-1 in skeletal muscle. On the other hand, CREB which localized in nucleus be the important rules to regulated mitochondrial biogenesis due its ability to increase PGC-1α as master regulation of mitochondrial biogenesis [30].

To determine this statements we interested to examined effect of H89 (PKA inhibitor) in order to prove effect of curcumin treatment to regulated mitochondrial biogenesis in skeletal muscle. Indeed, our result showed that H89 abolished effect of curcumin treatment to increases phosphorylation of LKB-1 and CREB. Furthermore, curcumin treatment additive effect of exercise to increases phosphorylation of LKB-1 and CREB and H89 abolished this effect. This evidence showed that PKA be the important rules on mitochondrial biogenesis in skeletal muscle through LKB-1 and CREB pathway. Our result also consistent with the other previous study that resveratrol-stimulated AMPK activity is abolished in LKB-1 deficient neurons [31]. In contrast, HeLa cells, which are deficient in LKB1 and represent a natural "knock-out" cell line [32,33], showed significantly less phosphorylation of both LKB1 and AMPK when treated with polyphenols, implying the importance of LKB1 in polyphenol action. Indeed our result also indicated that H89 have ability to abolished effect of curcumin treatment to increase phosphorylation of LKB-1. This result strengthen by previous evidence which determine that H89 suppression the ginsenoside metabolite 20-O-β-D-glucopyranosyl-20(S)-protopanaxadiol (GPD) mediated matrix metalloproteinase-1 (MMP-1) via inhibition of LKB-1 [34].

On the other pathway, CREB have ability to increase mitochondrial biogenesis in muscle cells through PGC-1α [35]. Furthermore, H89 inhibits the effect of CREB. Above result parallel with our result which showed result that H89 inhibit effect of exercise to increase phosphorylation CREB on rodent skeletal muscle. The important section from our result showed evidence that curcumin treatment

additive of exercise. Previous study had found that, in rat red quadriceps, the major metabolic regulatory molecules LKB1 and PGC-1α increase over time through 53 days of endurance training may play roles in maintaining the increased skeletal muscle mitochondrial mass resulting from endurance training [36]. Based on above result we suggested that PKA inhibitor H89 inhibit phosphorylation of LKB-1 and CREB involved in effect of curcumin and together with exercise on skeletal muscle.

4. Curcumin treatment inhibit phosphorylation of PDE4A to increase cAMP levels in rodent skeletal muscle

Previous studies have shown that forskolin (adenylyl cyclase activator) induces cAMP [37]. On the other way, inhibition of phosphodiesterase (PDE) by PDE inhibitor rolipram also increase cAMP [26]. Indeed, our results also indicated that curcumin seems to have an effect similar to that of rolipram on skeletal muscle and this evidence indicated that magnitude cAMP level due of these factors. Previous studies have shown that curcumin inhibits PDE in endothelial cells [38], pancreatic β-cells [39], and endothelial cells [40]. Furthermore, the polyphenol resveratrol causes an increase in cAMP concentration not by increasing cAMP production but by inhibiting cAMP PDEs, which hydrolyze cAMP to AMP [27]. Our evidence supports the idea that curcumin preferentially inhibits PDE to increase cAMP. Our results strengthened this statement because we determined that curcumin treatment alone and curcumin combined with exercise clearly decreased phosphorylation of PDE4A in skeletal muscle.

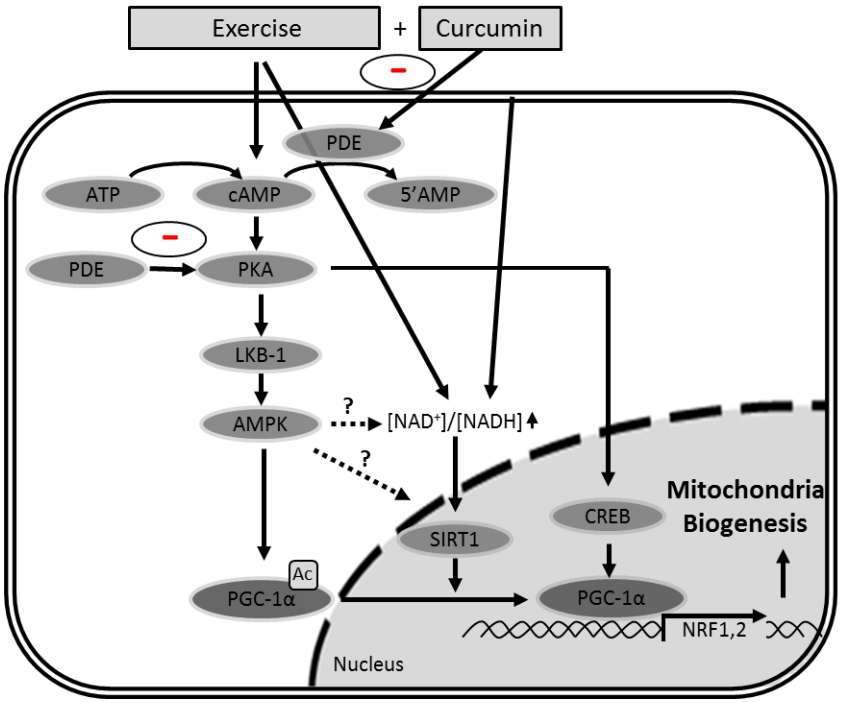


Figure 1. Curcumin Mechanism to Regulated Mitochondria Biogenesis on Skeletal Muscle

5. Conclusion

In conclusion, curcumin treatment together with exercise increased cAMP level in skeletal muscle through reduced phosphorylation of PDE4A. Furthermore, curcumin treatment together with exercise increased downstream targets of PKA, including phosphorylation of AMPK, deacetylated PGC-1α, and COX-IV expression in rodent skeletal muscle. Above result indicated that curcumin supplement showed potentially to increase human performance through its ability to increase mitochondrial biogenesis.

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