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Reviews

The effect of exercise on skeletal muscle glucose uptake in type 2 diabetes: An epigenetic perspective

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ABSTRACT

Changes in eating habits and sedentary lifestyle are main contributors to type 2 diabetes (T2D) development, and studies suggest that epigenetic modifications are involved with the growing incidence of this disease. Regular exercise modulates many intracellular pathways improving insulin resistance and glucose uptake in skeletal muscle, both early abnormalities of T2D. Mitochondria dysfunction and decreased expression of glucose transporter (GLUT4) were identified as main factors of insulin resistance. Moreover, it has been suggested that skeletal muscle of T2D subjects have a different pattern of epigenetic marks on the promoter of GLUT4 and PGC1, main regulator of mitochondrial function, compared with nondiabetic individuals. Recent studies have proposed that regular exercise could improve glucose uptake by the attenuation of such epigenetic modification induced at GLUT4, PGC1 and its downstream regulators; however, the exact mechanism is still to be understood. Herein we review the known epigenetic modifications on GLUT4 and mitochondrial proteins that lead to impairment of skeletal muscle glucose uptake and T2D development, and the effect of physical exercise at these modifications.

Abbreviations: 5caC, 5-carboxylcytosine; 5fC, 5-formylcytosine; 5hmC, 5-hydroxymethylcytosine; 5mC, 5-methylcytosine; A, alanine; Ac, Acetylation; AKT, Protein Kinase B; AMPK, 5' AMP-activated protein kinase; αKG, alpha-ketoglutarate; aPKC or PKCλ/ζ, atypical protein kinase C; AS160, substrate of 160KD of Protein Kinase B; BER, base excision repair; C2C12, mouse myoblast cell lines; CaMK, Ca2+/calmodulin-dependent protein kinase; CaMKK, Ca/calmodulin- dependent protein kinase kinase; DNAme, DNA methylation; DNMT, DNA methyltransferase; G, glycine; GLUT4, glucose transporter 4; H2A, histone 2A; H2B, histone B; H3, histone 3; H3ac, Histone 3 acetylation; H3K4me, histone 3 lysine 4 methylation; H3K9me, histone 3 lysine 9 mono-methylation; H4, histone 4; HAT, histone acetyltransferase; HbA1c, hemoglobin A1c; HDAC, histone deacetylase; HMT, histone methyl transferase; IR, insulin receptor; IRS, insulin receptor substrate; K, lysine; Let-7, microRNA let-7; MEF2, myocyte enhancer factor-2; Me, methylation; MiR-106b, microRNA 106b; MiR-23a, microRNA 23a; miRNA, microRNA; NRF1/2, nuclear respiratory factors ½; PGC1, peroxisome proliferator-activated receptor gamma, coactivator 1 alpha; PI3K, phosphatidylinositol (PI)-3-kinase; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; PPARα, peroxisome proliferator-activated receptor alpha; Ps, phosphorylation; Q, glutamine; R, arginine; S, serine; SAM, S-adenosyl methionine; SIRT1, sirtuin 1; Su, sumoylation; T, threonine; T2D, type 2 diabetes; TET, Ten-eleven-translocation enzymes; TFAM, mitochondrial transcription factor A; TDG, thymine-DNA glycosylase; Ub, ubiquitination.

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1. Introduction

Type 2 diabetes (T2D) has become a slow growing pandemic of the 21st century with prevalence and projections increasing every year [1,2]. Interestingly in the last decade the projections were that T2D could reach 366 million subjects by 2030 [3], nevertheless according to more recent reports this number could rise by 50%. In 2011 the International Diabetes Federation estimated that about 552 million worldwide subjects will be diabetic by 2030 [4].

Considering that the main cut points for T2D diagnosis have not changed since 2002, e.g. fasting plasma glucose higher than 126 mg/dl and HbA1c level of 6.5%, the worldwide changes in eating habits and the sedentary lifestyle are the main contributors for the increased rates of T2D [5,6]. This fact is easily observed in countries that recently opened the doors for the "western way of life". In China, T2D prevalence in 1980 was lower than 1%, but presently this country has emerged as the worldwide 'diabetes epicenter'. In 2009, 92 million adults (9.7% of the total population) had diabetes and another 148.2 million adults (15.5% of the total population) had classified pre-diabetes [1]. This growing prevalence seems to be the result of rapid economic urbanization added with the nutrition and behavior transition in a short period, over the last 30 years.

From a biological perspective, epigenetic modifications are the link that better explains how these new external changes could have long-lasting effect on the metabolism and health contributing to the growing prevalence of T2D [5]. In fact, there has been considerable interest among the scientific population on how environmental factors modulate epigenetic modifications, and how it controls transcription and cell phenotype (Fig. 1). During the last decades, some possible mechanisms related to epigenetic changes and the development of T2D have been described, however there are many sub-mechanisms and pathways that are not completely understood.

One of the main therapeutic approaches towards T2D is the improvement of lipid profile and the daily control of the glycemic levels, and fortunately it is well described that regular exercise can regulate these parameters [3,7]. In fact, studies suggest that exercise could diminish high caloric food intake improving metabolic profile [8,9] and skeletal muscle contraction can increase glucose uptake and lipid peroxidation [10–12]. However, the global factors regulating physical exercise-induced changes in skeletal muscle of obese and insulin resistance individuals are unknown. Moreover, a number of reviews have addressed in general the relationship of epigenetic modifications induced by exercise with the potential improvements on T2D [13–17] but the exact link with skeletal muscle glucose uptake is still a blind spot. Therefore, in this review we analyze the latest studies that aimed to verify the effect of exercise and muscle contraction on the development of T2D by the improvement on insulin sensibility and glucose transport in skeletal muscle. Since the effect of endurance exercise on glucose uptake is better characterized compared to resistance exercise, this review will focus on studies that analyzed the role of endurance exercise and muscle contraction, on epigenetic modifications in T2D.

2. Epigenetics Modifications

Epigenetic modifications are long-term alterations on the "*epi*" (from the Greek: over, outside of or around) -gene that modifies the transcriptional potential of a cell. These modifications do not affect the coding sequence of DNA but epigenetic modifications *per se* can alter protein expression and cellular phenotype according to signals from local environment, by cell-to-cell interaction or soluble factors. These signals can induce adaptive responses that can prompt suitable gene expression for replication, differentiation and apoptosis depending on the cell type and developmental context [5,18]. Recent studies have shown that epigenetic modifications play a major role in many acquired chronic diseases, as T2D, whereas small changes in the *epi*-genome can change cell phenotype leading to the manifestation of the disease [19,20]. DNA methylation, histone modifications, and noncoding RNA activity are the three major epigenetic mechanisms identified to regulate gene expression [20].

DNA methylation is the addition of a methyl group on the position 5 of cytosine and this binding cooperates with N-

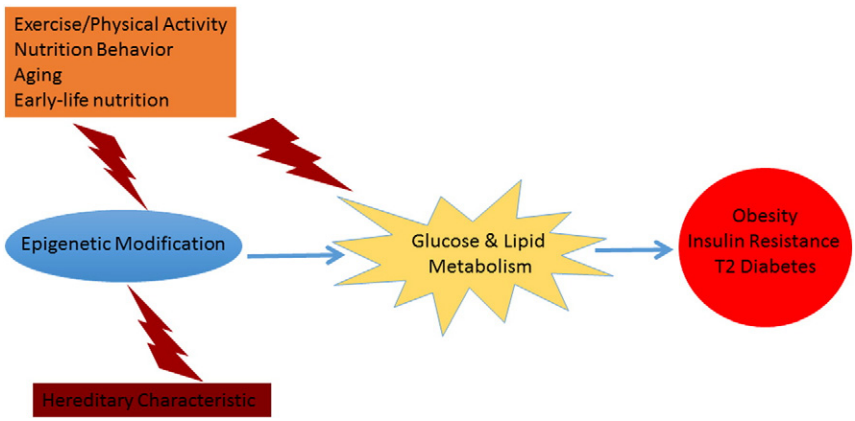

Fig. 1 – *Risk factors and T2D*. Risk factors that may act through epigenetic mechanisms that impair glucose and lipid metabolism that induce insulin resistance and diabetes type 2 (T2D).