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Glycation of Myosin - In Aging & Diabetes. How to Help Out?: A Mini Review.

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ABSTRACT

The effect of nonenzymatic glycosylation (glycation) on the structure and function of extracellular proteins have been studied extensively, but, that on intracellular proteins is, less well known. Hence, a review of the scientific literature of the same on myosin was undertaken. Many articles related to the work on glycation of Myosin in Diabetes Mellitus & aging have been reviewed & the results are compiled here. The results of the studies reviewed show that there are changes in both the structural and functional properties of the protein, myosin due to glycation. Change in the structural conformation was detected by Matrix-assisted laser desorption/ionization (MALDI) mass spectrometry. Reduction in the functional ability i.e.. reduced motility was detected by a single-fiber in vitro motility assay. Glutathione reversed the early glycation effects by acting as a nucleophile cleaving the Schiff-base adduct similar to Hydroxylamine hydrochloride. Exercise also partially reverses this & strengthens the muscles even in the elderly persons. Glycation of myosin in Diabetes & aging results in change in the structural conformation of the protein leading to reduced functional ability & that can be reversed in early stages by proper food & exercise.

Keywords: exercise, glutathione, glycation, myosin

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INTRODUCTION

Skeletal Muscle protein, Myosin constitutes 15–25% of the total body protein & has a half-life as long as 30 days [1]. It is a large molecule (540kD) with 6 polypeptide chains of which 2 are heavy & 4 are light chains. It has 2 portions as heavy meromyosin (HMM) & light meromyosin (LMM). The LMM can form filaments but has no enzymatic activity. HMM acts as the enzyme ATPase. It binds to actin polymer & promotes muscle contraction through hydrolysis of ATP but, cannot form filaments. HMM portion can be split into 2 fragments- S1 & S2. S1 fragment has the ATPase site & the actin binding site [2]

Myosin turnover rate decreases with aging as observed in human muscle. This slow turnover rate results in myosin getting glycosylated nonenzymatically(glycation). Intracellular glycating agents are the glycolytic intermediates such as glucose-6-phosphate & glyceraldehyde-3-phosphate and to a lesser extent glucose. A chemical reaction between the free aldehyde groups of sugars and the amino groups of the free lysine residues of proteins form reversible Schiff base adducts. Subsequent Amadori rearrangement of these generate irreversible Advanced Glycation End products (AGEs) & free radical-mediated oxidation augments the formation of AGEs [3]

Glycation of myosin in old age & diabetes leads to impairment in muscle function. Myosin is rich in potential sites for glycation as it has 201 lysine residues. 2 such regions are actin binding site and the ATPase catalytic site. Glycation in the actin binding site affects the actin-activated ATPase activity & that in ATPase catalytic site affects the rate of ADP release and actin filament speed. Glycation of S1 fragment of myosin reduces the ATPase activity thus reducing the function [4].

AGEs are compounds formed by the nonenzymatic, irreversible glycation of proteins, lipids, nucleic acids etc. They accumulate in tissues as age advances and with increasing concentration of sugar[5,6]. Hence, AGEs increase the risk of developing many chronic diseases that affect elderly persons. They damage the tissues by triggering inflammation & causing cross-linking of proteins like collagen [7]. AGEs ingested in foods (foods exposed to very high temperatures, ionization and irradiation) also contribute to the ill effects[8]. AGEs also increase GSSG, the redox component in vitro. In skeletal muscle, the glutathione peroxidase system is operative to scavenge singlet oxygen and hydroxyl radicals formed excessively during exercise, infection, or disease due to oxidative stress and lipid peroxidation. GSH - Reverses early effects of glycation on myosin function by its antioxidant activity.

MATERIALS AND METHODS

Many articles related to the research work on the effects of glycation of Myosin in Diabetes Mellitus & Old age have been published in the recent past. A review of this scientific literature was undertaken to understand those effects & identify the remedial measures & the results of the studies as shown in them are compiled here.

RESULTS AND DISCUSSION

Reviewed articles reveal that Glycation of myosin resulted in change in the structural conformation of Myosin & Reduction in the functional ability of Myosin as detected by MALDI mass spectrometry and single-fiber in vitro motility assay.

Matrix-assisted laser desorption/ionization (MALDI) mass spectrometry [9] - identified glycation - related structural alterations in myosin (extracted from young male Wistar rats) exposed to glucose for longer periods as disappearance of specific Lys-C proteolysis products & appearance of higher mass peaks due to cross-linking by glucose.

Glycation blocked proteolysis at sites where lysine modification occurred, leading to higher mass products of glycation. Moreover, glycation led to intramolecular cross-linking also giving rise to higher mass products[1].

These high mass products disappear after treatment with a Schiff base-cleaving agent, hydroxylamine hydrochloride.

Early glycation products in the regulatory regions of myosin molecule cause reduction in the in vitro motility speed of the muscle. This is reversed by Schiff base-cleaving agent hydroxylamine hydrochloride [4].

Unlike many tissues, antioxidant enzyme activities including GPX (Glutathione Peroxidase) increase in skeletal muscle with age due to an increase in the insults of oxidative stress. GSH contents in the slow-twitch oxidative rat soleus is estimated to be higher than that in erythrocytes, lung & brain tissue. AGEs cause a dose-dependent and long-term increase in GSSG in vitro. GSH degrades early glycation products as a strong nucleophile similar to hydroxylamine hydrochloride that displaces glucose & other potential carbonyl compounds, from Schiff base adducts at the lysine residues of myosin. Hence, the decrease in efficacy of GSH in controlling the formation of AGEs in aged tissue. Effect of glutathione on glycated myosin function, using a single-fiber in vitro motility assay showed restored motility [10].

Myosin heavy-chain synthesis rate declined with age as observed in a study involving radiolabelled Leucine infusion to subjects from 20 to 92 years of age [11]. In another study with rats, the number of reactive cysteines in HMM (Heavy Mero Myosin) significantly decreased with age & chemical changes in myosin (probably oxidation of cysteines) led to inhibitory effects on actin-activated myosin ATPase. These contribute to the decline in muscle mass & contractile function in the elderly [12] AGEs stimulate cytokine & reactive oxygen species production through AGE-specific receptors & modify intracellular proteins & may potentially affect skeletal muscle. E.g.: Women with high serum carboxymethyl-lysine (CML), a dominant AGE, have greater muscle weakness [13].

Mitochondrial dysfunction associated with the accumulation of mitochondrial DNA deletions and sarcopenia were seen in single fibers isolated from skeletal muscle in a number of species including humans [14].

A study on Skeletal muscle biopsies from healthy older & younger adults showed reduced muscle strength in the elderly. Some had muscle samples taken before and after a six-month resistance exercise-training program. Older adults were weaker than younger by 59% before exercise training and only 38% lower after six months of training as the strength improved significantly [14,15].

CONCLUSION

Glucose modifies myosin function in a dose-dependent manner and that glutathione reverses the effect of glucose on myosin function.

An avoidance of foods rich in deranged proteins and peptides, and the consumption of antioxidants will help to prevent AGEs formation.

Circulating levels of AGEs can be reduced by drug treatment with AGE inhibitors and AGE breakers. Reduced muscle strength can be partially reversed by resistance exercise training.

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