Effects of short-duration skeletal muscle exercise on glycogen synthesis in obesity during hyperinsulinemia. A study using ^{13}C-Magnetic Resonance Spectroscopy

J. H. de Haan[1], A. Mulder[2], P. Smits[3], C. J. Tack[2], A. Heerschap[1]

[1]Dept. of Radiology, UMC Nijmegen, Nijmegen, Netherlands, [2]Dept. of General Internal Medicine, UMC Nijmegen, Nijmegen, Netherlands, [3]Dept. of Pharmacology, UMC Nijmegen, Nijmegen, Gelderland, Netherlands

Abstract

During hyperinsulinemia, exercise strongly stimulates glycogen synthesis in skeletal muscle of healthy subjects. However, little is known about the additional effect of exercise in obesity upon insulin stimulated glucose uptake. Ten obese subjects underwent a euglycemic hyperinsulinemic clamp for 150 min, with simultaneous measurement of glycogen in skeletal muscle. A short exercise increased the rate of glycogen synthesis rate ~165% compared to ~317% in healthy subjects. Blood flow had no relation with these increases. The glycogen synthesis rate after exercise under hyperinsulinemic condition is reduced in obesity, independent of age. These results indicate that in humans, insulin and exercise mediated glucose uptake are interrelated.

Introduction

Inadequate glucose uptake in muscle is the hallmark of diabetes. Insulin resistance is also observed in obesity. Glucose uptake is not only stimulated by insulin, but also by exercise, presumably by translocation of glucose transporter 4 (GLUT 4) [1]. Little is know about the additional effect of exercise upon insulin stimulated glucose uptake in obese humans. Glycogen synthesis is reduced in obesitas during hyperinsulinemia [2]. ^{13}C-MRS provides a method that enables continuous, non-invasive measurement of glycogen synthesis in skeletal muscle in humans [3, 4]. In this study, we measured the effect of a short bout of exercise on insulin-induced glycogen synthesis in skeletal muscle in obese subjects. Because we hypothesised that exercise may change blood flow and thereby increase substrate to the target cells, we also measured blood flow responses to exercise in a separate experiment.

Methods

Ten obese subjects (five young: mean age 24.6 ± 2.2, BMI 30.8 ± 3.0, five elderly: mean age 56.8 ± 5.1, BMI 36.2 ± 3.8) underwent a euglycemic hyperinsulinemic clamp (430 pM/m^2/min insulin, infusion of 20% glucose, 30% enriched with 1-^{13}C-glucose) for 150 min, with simultaneous measurement of glycogen in skeletal muscle. During the measurements, the subjects were lying inside the MR magnet (1,5 T Magnetom Vision , Siemens Erlangen) with the gastrocnemius muscle of the right leg positioned on top of a concentric surface coil probe for ^{13}C acquisition. For ^{1}H acquisition, decoupling, and shimming a quadrature coil was used. ^{13}C MR spectra were obtained in 15-min blocks consisting of 2500 scans using an adiabatic pulse and a repetition time of 180 ms. During acquisition in the first 60 ms continuous wave decoupling at 26 W was applied. Glycogen synthesis rate is determined as the increase in glycogen signal in time, corrected for plasma 1-^{13}C-glucose enrichment level. Glycogen, glucose and creatine levels were determined of the musculus gastrocnemius (calf muscle). After baseline measurements, all subjects performed acute exercise of the calf muscle (two 1-minute periods of single-legged toe lifting separated by 1 minute of rest) [4]. MRS measurements were subsequently continued for at least 50 min. On a separate day, the whole experiment was repeated without MRS measurement. Blood flow at baseline, during insulin and before and after exercise was measured using strain-gauge plethysmography in the exercised leg, the control leg and the right forearm.

Results:

Increase in the glycogen signal at 100.5 ppm before and after exercise demonstrated a good linear relation in time ($r^2 > 0.95$). Baseline insulin-stimulated glycogen synthesis rate was 0.22 ± 0.05 A.U./min in old obese subjects and 0.30 ± 0.05 A.U./min. (significantly higher, $p<0.05$) in young obese subjects. Exercise increased the rate of glycogen synthesis substantially to 0.35 ± 0.05 in the old obese group ($p<0.05$) and to 0.53 ± 0.02 A.U./ min ($p<0.05$) in the young obese group, both an increase of ~165%, compared to 317% in young healthy subjects (figure 1). A strong correlation ($r = 0.77$; $p= 0.0006$) was found between the whole body glucose uptake or M-value of all subjects and the increase in glycogen synthesis due to exercise (figure 2). After exercise, calf blood flow in the exercised leg of three old obese increased from 2.21 ± 1.08 to 12.43 ± 4.34 ($p< 0.001$) mL/dL/min, but blood flow returned to 2.6 ± 0.70 within 30 minutes and further decreased afterwards, while the increase in glycogen synthesis was stable and still ongoing.

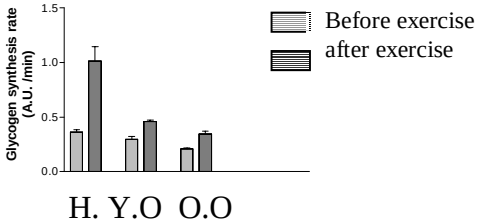

Figure 1: glycogen synthesis rate before and after exercises in three different groups: H = healthy; Y.O. = young obese; O.O. = old obese All increases are significant ($p<0.05$)

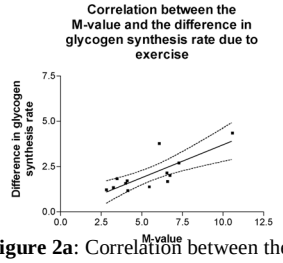

Figure 2a: Correlation between the whole body glucose uptake (M-value) and increased glycogen synthesis rate due to exercise of all measured subjects. R = 0.77; p=0.0006

Discussion:

These results indicate that in humans, a short bout of exercise has an acute effect on the glycogen synthesis rate under hyperinsulinemic conditions. The glycogen synthesis rate after exercise under hyperinsulinemic condition is reduced in obesity, independent of age. Although exercise was a strong stimuli for vasodilatation, the lack of a temporal relationship between the increase and subsequent decrease in blood flow and the linear increase in glycogen synthesis rate argue against a direct causal effect. The similarity of the reduced effects of exercise in obesitas, suggests that the insulin and exercise mediated glucose uptake share a common pathway. Since in healthy humans glucose transport is the rate limiting step in glycogen synthesis, the reduced glucose uptake enhancing effect of exercise under hyperinsulinemia in obesity suggests an reduced additional translocation of GLUT4 to the cell membrane in obesitas.

References

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