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

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**Abstract**

Not only insulin, but also exercise and ischemia stimulate glucose uptake in skeletal muscle. Little is known about the additional effect of exercise or ischemia upon insulin stimulated glucose uptake. Ten healthy subjects underwent a euglycemic hyperinsulinemic clamp for 150 min, with simultaneous measurement of glycogen in skeletal muscle. Exercise increased the rate of glycogen synthesis rate ~300%. Ischemia increased glycogen synthesis rate ~200%. Blood flow had no relation with these increases. These results indicate that in humans, either a short bout of exercise or ischemia have an acute effect on the glycogen synthesis rate under hyperinsulinemic conditions.

**Introduction**

Inadequate glucose uptake in muscle is the hallmark of diabetes. This uptake is not only stimulated by insulin, but also by exercise and ischemia, presumably by translocation of glucose transporter 4 (GLUT 4) [1]. Little is know about the additional effect of exercise or ischemia upon insulin stimulated glucose uptake in humans. In dog-hearts ischemia was found to increase uptake in addition to the effect of insulin [2]. $^{13}$C-MRS provides a method that enables continuous, non-invasive measurement of glycogen synthesis in skeletal muscle in humans [3]. In this study, we measured the effect of a short bout of exercise or ischemia on insulin-induced glycogen synthesis in skeletal muscle. Because we hypothesised that exercise/ ischemia 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 healthy subjects (mean age 20.9 ± 1.6, BMI 21.4 ± 1.4) 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 spectrometer (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 5000 scans using an adiabatic pulse and a repetition time of 180 ms. During acquisition in the first 60 ms continuous wave (CW) 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, five subjects performed acute exercise of the calf muscle (two 1-minute periods of single-legged toe lifting separated by 1minute of rest) [4] and five subjects underwent ten minutes of ischemia (upper leg cuff inflated to suprasystolic pressure). 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/ ischemia was measured using strain-gauge plethysmography in the exercised/ ischemic leg, the control leg and the right forearm.

**Results:**

From measurements of the increase in the glycogen signal at 100.1 ppm (figure 1) before and after exercise/ ischemia a good linear relation in time ($r^2 > 0.95$) was obtained as shown in figure 2a. Baseline insulin-stimulated glycogen synthesis rate was 0.33 ± 0.08 AU/min. Exercise increased the rate of glycogen synthesis rate substantially to 1.01 ± 0.28 A.U./ min ($p<0.01$), an increase of ~300%. After exercise, calf blood flow in the exercised leg increased from 1.58 ± 0.35 to 17.13 ± 5.3 ($p< 0.001$) mL/dL/min, but blood flow returned to 2.8 ± 0.5 within 30 minutes and further decreased afterwards (figure 2b), while the increase in glycogen synthesis was stable and still ongoing.

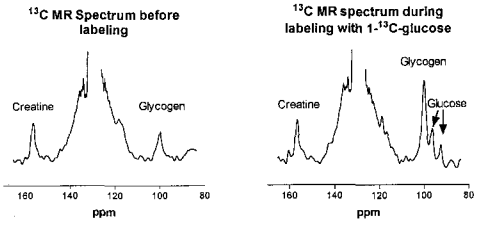


**Figure 1**: $^{13}$C MR spectra before and during infusion with 1-$^{13}$C-glucose

Ischemia increased glycogen synthesis rate from 0.32 ± 0.09 AU/min (=similar to the pre-exercise level) to 0.63 ± 0.22 AU/min ($p= 0.03$), an increase of ~200%. Blood flow increased from 1.31 ± 0.49 to 5.26 ± 2.36 ($p= 0.006$) mL/dL/min but returned to baseline within 20 minutes.

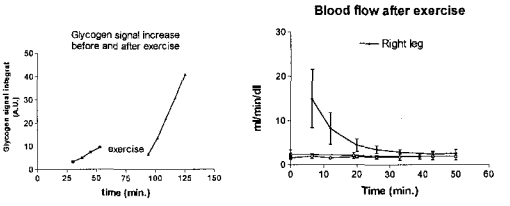


**Figure 2a:** Typical glycogen synthesis before and after exercise. b) blood flow before and after exercise. Also as control, right arm and left leg were measured.

**Discussion:**

These results indicate that in humans, either a short bout of exercise or ischemic period have an acute effect on the glycogen synthesis rate under hyperinsulinemic conditions. Although both exercise and ischemia were 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 effects of exercise and ischemia, suggests that the same pathway is involved; e.g. one in which 5'-AMP-activated kinase plays a key role. Since in healthy humans glucose transport is the rate limiting step in glycogen synthesis, the glucose uptake enhancing effect of exercise/ ischemia under hyperinsulinemia suggests an additional mechanism of translocation of GLUT4 to the cell membrane.

References

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