



Mismatch between skeletal muscle glucose delivery, interstitial concentration and membrane permeability may limit insulin sensitivity after exercise

Glenn McConell¹, Kim Sjøberg², Frederik Ceutz², Lasse Gliemann², Michael Nyberg², Ylva Hellsten², Christian Frøsig², Bente Kiens², Jørgen Wojtaszewski², Erik Richter²

1. Victoria University
2. University of Copenhagen

Objective The relationship between skeletal muscle perfusion, interstitial glucose concentration and sarcolemmal permeability to glucose in exercise-induced increases in muscle insulin sensitivity is not well established. A single bout of exercise increases skeletal muscle insulin sensitivity through coordinated increases in insulin-stimulated microvascular perfusion and insulin signalling. Reducing leg and muscle microvascular blood flow with local nitric oxide synthase (NOS) inhibition during a hyperinsulinaemic euglycaemic clamp reduces leg glucose uptake in a previously exercised, but not in a contralateral non-exercised leg, without affecting insulin signalling in either leg (Sjøberg *et al.* 2017). Therefore, it is possible that the reduction in muscle perfusion decreases muscle interstitial glucose concentration to a point that limits skeletal muscle insulin-stimulated glucose uptake following exercise. We examined this using microdialysis of vastus lateralis muscle.

Methods Ten healthy males (Age: 27±1 yr., Weight: 77.7±2.3 kg, BMI 23.9±0.5, VO₂ peak: 50.7±1.5 ml·kg⁻¹·min⁻¹) performed 60 min of 1-legged knee extensor exercise at 80% of 1-legged peak work load with three 5 min intervals at 100% 1-legged peak work load. Participants then rested for 4 hours and catheters were inserted into the femoral artery and vein of both legs for subsequent measurement of leg glucose uptake and for femoral artery infusion of the NOS inhibitor *NG*-monomethyl L-arginine acetate (L-NMMA) and the vasodilator ATP. Catheters were also placed in antecubital veins for infusion of insulin and glucose. Three microdialysis catheters, with a semi-permeable membrane the length of 30 mm and a molecular cut-off at 20,000 dalton, were inserted into the vastus lateral muscle of both legs. Glucose and D-[6-³H(N)]glucose were added to the perfusate. Four hours after discontinuing the exercise a 225 minute euglycaemic hyperinsulinaemic clamp was initiated (insulin infusion 1.4 mU·kg⁻¹·min⁻¹). Ninety min into the clamp L-NMMA was infused at a constant rate (0.4 mg·kg⁻¹ leg mass·min⁻¹) into both femoral arteries for 45 min. The insulin infusion was maintained for another 90 min and during the last 45 min ATP (0.3 μmol·ml⁻¹) was infused locally into both femoral arteries at a rate of 200-350 μl·min⁻¹ to obtain a leg blood flow that was double the blood flow during insulin only infusion. A second control protocol was undertaken that was identical in regards to exercise and recovery but no insulin, L-NMMA or ATP was infused.

Results During the clamp leg glucose uptake and leg blood flow were higher (P<0.05) in the previously exercised than the control leg whereas the interstitial glucose concentration decreased to lower (P<0.05) values in the exercised (~3.1mM) than the control (~4.8mM) leg. Estimated sarcolemmal glucose permeability was twice as high (P<0.05) in the exercised compared with the rested leg. The NOS inhibitor L-NMMA decreased LBF in both legs and interstitial glucose concentration dropped to ~2.3 mM in the exercised but only to ~3.7 mM in non-exercised muscle. This abrogated the augmented effect of insulin on LGU in the exercised leg while apparent sarcolemmal permeability to glucose remained unchanged with L-NMMA in both legs. Doubling leg blood flow by local infusion of ATP increased leg glucose uptake in both legs without any major change in interstitial glucose concentration or sarcolemmal permeability to glucose.

Conclusions These findings suggest that during flow restriction due to L-NMMA, the interstitial glucose concentration becomes limiting for leg glucose uptake in exercised but not in non-exercised muscle. Therefore, the vasodilatory effect of insulin is an important component of the increased insulin sensitivity to stimulate glucose uptake following exercise by limiting the drop in the interstitial glucose concentration that occurs due to the increased sarcolemmal permeability to glucose.

Reference

Sjoberg, K. A., C. Frosig, R. Kjobsted, L. Sylow, M. Kleinert, A. C. Betik, C. S. Shaw, B. Kiens, J. F. P. Wojtaszewski, S. Rattigan, E. A. Richter, and G. K. McConnell. Exercise Increases Human Skeletal Muscle Insulin Sensitivity via Coordinated Increases in Microvascular Perfusion and Molecular Signaling. *Diabetes* 66: 1501-10, 2017.