Skeletal muscle interstitial glucose concentration becomes limiting to glucose uptake during insulin exposure after exercise in humans

G.K. McConell,[1] K.A. Sjøberg,[2] F. Ceutz,[2] L. Gliemann,[2] M. Nyberg,[2] Y. Hellsten,[2] C. Frøsig,[2] B. Kiens,[2] J.F.P. Wojtaszewski[2] and E.A. Richter,[2] [1]Institute of Sport, Exercise and Active Living (ISEAL), Victoria University, Melbourne, VIC 8001, Australia and [2]Section of Molecular Physiology, Department of Nutrition, Exercise and Sports, University of Copenhagen, Denmark.

A single bout of exercise increases skeletal muscle insulin sensitivity through coordinated increases in insulin-stimulated microvascular perfusion and insulin signalling (Sjoberg *et al.*, 2017). 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 (Sjoberg *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.

Ten healthy males (Age: 27±1 yr., Weight: 77.7±2.3 kg, BMI 23.9±0.5, VO_2 peak: 50.7±1.5 $ml \cdot kg^{-1} \cdot min^{-1}$, mean±SEM) 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 $mU^{-1}kg^{-1}min$). Ninety min into the clamp L-NMMA was infused at a constant rate (0.4 $mg \cdot kg^{-1}$ leg $mass \cdot min^{-1}$) 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 $\mu mol \cdot ml^{-1}$) was infused locally into both femoral arteries at a rate of 200-350 $\mu l \cdot min^{-1}$ to obtain a leg blood flow that was double the blood flow during insulin only infusion.

Skeletal muscle interstitial glucose concentration decreased ($P<0.05$) more during the first 90 min of the insulin infusion in the previously exercised leg (to 3.0±0.3 $mmol \cdot L^{-1}$) compared with the contralateral non-exercised leg (to 4.6±0.3 $mmol \cdot L^{-1}$). Reducing leg blood flow during the insulin infusion ($P<0.05$) with local femoral artery L-NMMA infusion into both legs significantly reduced interstitial glucose concentration in the previously exercised leg to a level (2.2±0.4 $mmol \cdot L^{-1}$) which was paralleled by a significant reduction in insulin-stimulated glucose uptake. In the non-exercised leg, interstitial glucose concentration only decreased ($P<0.05$) to 3.5±0.3 $mmol \cdot L^{-1}$ during L-NMMA and leg glucose uptake did not decrease compared with insulin infusion alone ($P>0.05$). After the cessation of the L-NMMA infusion, addition of local femoral ATP infusion to the insulin infusion resulted in a doubling ($P<0.05$) of leg blood flow and a restoration of skeletal muscle interstitial glucose concentration in the previously exercised leg back to the pre L-NMMA level (to 3.2±0.4 $mmol \cdot L^{-1}$). This resulted in a significant increase in leg glucose uptake above that of insulin infusion alone.

These results suggest that increased insulin sensitivity following acute exercise is dependent on an insulin-stimulated increase in muscle perfusion which maintains the skeletal muscle interstitial glucose concentration at a level that does not limit insulin-stimulated glucose uptake.

Sjøberg KA, Frøsig C, Kjøbsted R, Sylow L, Kleinert M, Betik AC, Shaw CS, Kiens B, Wojtaszewski JFP, Rattigan S, Richter EA, McConell GK. (2017). Exercise increases human skeletal muscle insulin sensitivity *via* coordinated increases in microvascular perfusion and molecular signaling. *Diabetes* **66**, 1501-10.