Local infusion of a nitric oxide synthase inhibitor reverses increases in leg insulin sensitivity after acute exercise in humans

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Background: Exercise training increases insulin sensitivity and reduces the risk of diabetes. The adaptations to exercise training are considered to largely reflect an accumulation of adaptations/perturbations from a series of acute exercise bouts. Indeed, insulin sensitivity is increased 4 hours after an acute exercise bout in normal healthy individuals. The mechanism(s) responsible for the increase in insulin sensitivity after acute exercise are unclear. We have shown that nitric oxide (NO) plays a role in skeletal muscle glucose uptake during exercise in rodents and in humans. In addition, we have evidence in rodents that NO may also have a role in insulin sensitivity after contraction.

Aims: The aim of this study was to determine whether local infusion of a NO synthase inhibitor attenuates the increase in leg insulin sensitivity 4 hours after prolonged single-legged exercise in healthy men.

Methods: Nine young healthy male participants were familiarised to submaximal one-legged knee extensor exercise before undertaking a single-legged VO_2 peak test. On a separate day they attended the laboratory in the morning in a fasted state and undertook one hour of one-legged extensor exercise. Catheters were then inserted into a forearm vein of both arms and a hand vein and cannulas were inserted into the femoral artery and femoral vein of both legs. Four hours after the exercise, participants were infused with glucose and insulin to perform a euglycaemic hyperinsulinaemic clamp for 195 mins. After 90 min of the clamp the NO synthase inhibitor NG-monomethyl-L-arginine (L-NMMA) was infused (0.45 mg/min/kg leg mass) into both femoral arteries for 45 min and then stopped while the clamp continued for a further 60 min. In both legs, leg blood flow was measured in the femoral artery (Doppler ultrasound) and blood samples were obtained from both femoral arteries and both femoral veins and muscle biopsies were obtained from both legs immediately prior to the clamp, after 60 min of the clamp and after 45 min of L-NMMA infusion.

Results: Leg glucose uptake increased in both legs during the clamp and was significantly ($P<0.05$) higher in the exercised leg compared with the non-exercised leg. Infusion of the NOS inhibitor during the insulin clamp significantly ($P<0.05$) reduced leg blood flow to a similar extent in both legs. The NOS inhibitor had no significant effect on leg glucose uptake during the insulin clamp in the previously rested leg. Remarkably, however, the NOS inhibitor attenuated ($P<0.05$) the increase in leg glucose uptake during the insulin clamp in the exercised leg so that it was not different to the rested leg. This appeared to be largely due to the NOS inhibitor reducing ($P<0.05$) leg blood flow during the insulin clamp as there was no significant effect of NOS inhibition on the activation of insulin signalling in either leg (pAKT Thr^{308}, pTBC1D4 Ser^{704}, pTBC1D4 Thr^{642}, pTBC1D4 Ser^{588}, pTBC1D4 Ser^{318}, pTBC1D1 Thr^{590}, pPAK1 Thr^{423} and pPAK2 Thr^{402}). When infusion of the NOS inhibitor was stopped the greater insulin sensitivity in the previously exercised leg than the previously rested leg again became apparent.

Conclusion: Local femoral artery infusion of a NOS inhibitor reverses the increase in insulin sensitivity in the exercised leg compared with the rested leg and this appears to be due to effects on blood flow rather than muscle insulin signalling.