nNOS is necessary for normal increases in glucose uptake during contraction of skeletal muscle

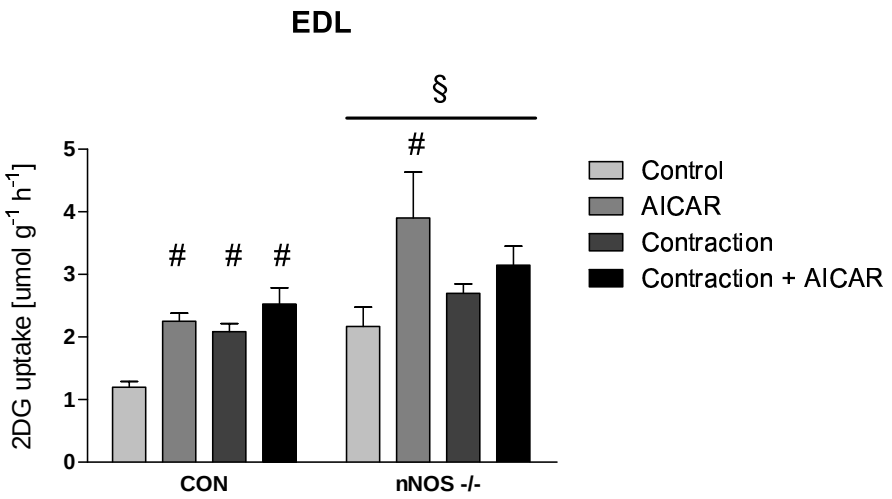
K. Linden, J.G. Ryall, C. van der Poel, J.D. Schertzer, G.S. Lynch and G.K. McConell, Department of Physiology, The University of Melbourne, VIC 3010, Australia.

People with type 2 diabetes have reduced skeletal muscle glucose uptake in response to insulin, however, glucose uptake during exercise is normal. The factors regulating skeletal muscle glucose uptake during exercise are unclear. We have evidence to suggest that nitric oxide (NO) plays a role in humans, however, evidence in rodents is conflicting. We examined glucose uptake in response to contraction and in response to the AMP-activated protein kinase (AMPK) activator AICAR (2 mM) in nNOS null mice (nNOS-/-, on a C57 Bl/6 background) and in C57Bl/6 control mice (CON). It has been shown the there is no increase in cGMP content in response to contraction in nNOS-/- mice.

Extensor digitorum longus (*EDL*) and *soleus* muscles from adult CON and nNOS-/- mice (n = 8/group) were surgically excised from deeply anesthetized mice (Nembutal, 60 mg/kg i.p.). Muscles were stimulated to contract for either 10 minutes (*EDL*, 60 Hz, 350 ms, train rate 0.167) or 15 minutes (*soleus*, 60 Hz, 600 ms, train rate 0.167) and 2-Deoxy-D-glucose (2-DG) uptake was examined during contraction. GLUT1 and GLUT4 protein expression was examined in *tibialas* anterior muscle.

Basal 2-DG uptake was elevated ($p < 0.05$) in the nNOS-/- mice compared with the CON mice. There was no difference in GLUT1 protein expression, however, GLUT4 protein expression was elevated ~20% ($p < 0.05$) in the nNOS-/- mice. Contraction increased ($p < 0.05$) 2-DG uptake in both muscles in the CON mice. There was, however, no significant increase ($p > 0.05$) in 2-DG uptake during contraction in either the *EDL* or *soleus* of the nNOS-/- mice. AICAR increased 2-DG uptake similarly in the nNOS-/- mice and the CON mice.

These results indicate that skeletal muscle nNOS is required for normal increases in glucose uptake in response to contraction, but not in response to AICAR. They suggest that NO is a critical regulator of skeletal muscle glucose uptake during contraction.



#, Significantly different than control group of the same genotype ($p < 0.05$)
§, Main effect for genotype ($p < 0.05$).

Supported by the National Health and Medical Research Council of Australia.