

CALCIUM ELEVATES GLUT4 TRANSCRIPTIONAL ACTIVITY IN THE PRESENCE OF ELEVATED FATTY ACIDS

Authors: Julia G. King, Katherine W. Stephenson, and Terry E. Jones, PhD, Department of Physical Therapy, East Carolina University, Greenville, NC 27858

Exercise induces increase in glucose transporter 4 (GLUT4) in skeletal muscle and subsequently exercise is used as a therapy to treat diabetes. In contrast, there is evidence that a high-fat diet suppresses GLUT4 content in skeletal muscle. Investigations into transcriptional regulation of the GLUT4 promoter are on-going, but it has not been determined how the GLUT4 promoter would respond to exercise and fatty acids simultaneously. Using the full length human GLUT4 promoter with a luciferase reporter transfected into rat skeletal muscle (L6) cells, the following experiments were done. The transfected cells were exposed to caffeine to increase cytosolic calcium, one of the purported signals from exercise that increases cellular GLUT4 content. Caffeine exposure for 12 h caused a 69% increase ($p < 0.09 \times 10^{-8}$) in luciferase activity indicating increased transcriptional regulation of the GLUT4 promoter by calcium. Additionally, the transfected cells were exposed to oleate to determine if elevated fatty acids could be responsible for the suppression of GLUT4 content in skeletal muscle. With oleate exposure for 12 and 24 h there was a 37% decrease ($p < 0.01 \times 10^{-3}$) in luciferase activity for both time points indicating decreased transcriptional activation of the GLUT4 promoter by elevated fatty acids. We asked if calcium would alter the GLUT4 promoter's response to elevated fatty acids. Transfected cells were exposed to oleate for 24 h with addition of caffeine for hours 13-24. Luciferase activity of the oleate-exposed cells in response to caffeine was 66% higher ($p < 0.01 \times 10^{-6}$) than cells exposed only to oleate for 24 h. This result suggests that GLUT4 transcriptional activity responds to increased cellular calcium concentrations in the presence of elevated fatty acids. This finding enhances the value of exercise as a therapeutic treatment of Type II diabetes.