Electrical stimuli release ATP to increase GLUT4 translocation and glucose uptake via PI3K?-Akt-AS160 in skeletal muscle cells

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Skeletal muscle glucose uptake in response to exercise is preserved in insulin-resistant conditions, but the signals involved are debated. ATP is released from skeletal muscle by contractile activity and can autocrinely signal through purinergic receptors, and we hypothesized it may influence glucose uptake. Electrical stimulation, ATP, and insulin each increased fluorescent 2-NBD-Glucose (2-NBDG) uptake in primary myotubes, but only electrical stimulation and ATP-dependent 2-NBDG uptake were inhibited by adenosine-phosphate phosphatase and by purinergic receptor blockade (suramin). Electrical stimulation transiently elevated extracellular ATP and caused Akt phosphorylation that was additive to insulin and inhibited by suramin. Exogenous ATP transiently activated Akt and, inhibiting phosphatidylinositol 3-kinase (PI3K) or Akt as well as dominant-negative Akt mutant, reduced ATP-dependent 2-NBDG uptake and Akt phosphorylation. ATP-dependent 2-NBDG uptake was also inhibited by the G prot