Mitochondrial fragmentation impairs insulin-dependent glucose uptake by modulating Akt activity through mitochondrial Ca2+ uptake

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Insulin is a major regulator of glucose metabolism, stimulating its mitochondrial oxidation in skeletal muscle cells. Mitochondria are dynamic organelles that can undergo structural remodeling in order to cope with these everchanging metabolic demands. However, the process by which mitochondrial morphology impacts insulin signaling in the skeletal muscle cells remains uncertain. To address this question, we silenced the mitochondrial fusion proteins Mfn2 and Opa1 and assessed insulin-dependent responses in L6 rat skeletal muscle cells. We found that mitochondrial fragmentation attenuates insulin-stimulated Akt phosphorylation, glucose uptake and cell respiratory rate. Importantly, we found that insulin induces a transient rise in mitochondrial Ca2+ uptake, which was attenuated by silencing Opa1 or Mfn2. Moreover, treatment with Ruthenium red, an inhibitor of mitochondrial Ca2+ uptake, impairs Akt signaling without affecting mitochondrial dynamics. All together, these results suggest th