Metformin divergently regulates the unfolded protein response and reduces protein synthesis and autophagy in palmitate-treated myotubes

B.D. Perry,[1,2,3] J.A. Rahnert,[2,3] Y. Xie,[2] D. Espinoza,[2,3] B. Zheng,[2] P. Zhang[2] and S.R. Price,[2,3,4] [1]School of Science and Health, Western Sydney University, NSW 2560, Australia, [2]Department of Medicine, Renal Division, Emory University, Atlanta, GA 30307, USA, [3]Atlanta VA Medical Center, Decatur, GA 30033, USA and [4]Department of Biochemistry and Molecular Biology, Brody School of Medicine, East Carolina University, Greenville, NC 27834, USA.

Circulating levels of saturated fatty acids, such as palmitate (PA), are elevated in type II diabetes mellitus and can contribute to signaling which promotes skeletal muscle atrophy. In skeletal muscle, PA reduces myotube diameter, induces ER stress, impairs protein synthesis and induces autophagy. The PA-induced reduction in protein synthesis may be due to the phosphorylation of eIF2α and activation of the unfolded protein response (UPR). Despite the reported actions of AMPK agonists (*e.g.* AICAR) in relieving elevated ER stress and inducing autophagy, the role of metformin on ER stress, protein synthesis and autophagy remains poorly understood in skeletal muscle. We investigated the effects of PA and metformin on protein synthesis, ER stress and autophagy in C2C12 skeletal myotubes. PA (500 μM) reduced protein synthesis and increased eIF2α phosphorylation but did not alter phospho-$p70^{S6K}$. Unlike AICAR, metformin and PA co-treatment further reduced protein synthesis and increased p-eIF2α. Metformin amplified the PA-induced increase in ATF4 protein expression, but reduced XBP1 s and did not change the levels of CHOP and caspase-3 relative to PA alone, indicating that metformin selectively regulates UPR signaling. Surprisingly, metformin reduced autophagy, as indicated by a reduction in LC3BII, and reduced ATG5 and ATG12 mRNAs following PA treatment. These findings indicate that metformin divergently modulates UPR signaling and may lead to a reduction in autophagy in cultured skeletal myotubes.