"ER Stress Induced By Hydrogen Peroxide In C2C12 Cells"

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Abstract
Oxidative stress and endoplasmic reticulum stress (ER stress) are both involved in a number of diseases amongst which insulin resistance, Parkinson syndrome and atherosclerosis. Although, those stresses are often regarded in a separately way, it is known that they can be interrelated. Oxidative stress could lead to ER stress and vice versa as demonstrated by studies focused on the potential cross talk between the signaling pathways triggered by each of them in various cell types including mouse fibroblast cells, Chinese hamster ovary cells and mesencephalic cells. Skeletal muscle is a great provider of reactive oxygen species (ROS) and ER stress has been found to be present in skeletal muscle in certain conditions such as high-fat feeding and extreme endurance exercise. In agreement with those observations we have investigated the consequences of oxidative stress on ER stress in C2C12 myotubes. PURPOSE: To establish if oxidative stress, induced by hydrogen peroxide (H2O2), can lead t...

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Oxidative stress and endoplasmic reticulum stress (ER stress) are both involved in a number of diseases amongst which insulin resistance, Parkinson syndrome and atherosclerosis. Although, those stresses are often regarded in a separately way, it is known that they can be interrelated. Oxidative stress could lead to ER stress and vice versa as demonstrated by studies focused on the potential cross talk between the signaling pathways triggered by each of them in various cell types including mouse fibroblast cells, Chinese hamster ovary cells and mesencephalic cells. Skeletal muscle is a great provider of reactive oxygen species (ROS) and ER stress has been found to be present in skeletal muscle in certain conditions such as high-fat feeding and extreme endurance exercise. In agreement with those observations we have investigated the consequences of oxidative stress on ER stress in C2C12 myotubes. PURPOSE: To establish if oxidative stress, induced by hydrogen peroxide (H$_2$O$_2$), can lead to ER stress in C2C12 myotubes. METHODS: Myogenic C2C12 cells were grown until confluence and further differentiated for 4 days. Preliminary experiments were carried out to determine the optimal H$_2$O$_2$ dose and incubation period for inducing ER stress. A dose of 200µM and incubation periods of 4h and 17h were the most potent conditions for triggering ER stress and were used subsequently. Several downstream targets of the IRE1α and PERK pathways were analyzed at the protein level by western blot and at the mRNA level by qPCR. Three independent experiments were carried out. Unpaired Student t-test was used for the statistical analysis. RESULTS: After 4h H$_2$O$_2$ incubation, P-eIF2α increased 7.7 +/- 1.3 fold (p<0.05) whereas P-JNK did not change (0.8 +/- 0.2, ns). After 17h H$_2$O$_2$ incubation, BiP and IREα expressions increased 5.3 +/- 1.5 and 7.1 +/- 1.9 fold, respectively (p<0.05) whereas PDI did not change (0.89 +/- 0.17 fold, p>0.05). At the mRNA level, bip and atf4 increased 1.9 +/- 0.2 and 2.4 +/- 0.4 fold, respectively (p<0.05), whereas spliced xbp1 (0.90 +/- 0.2 fold) and unspliced xbp1 (0.8 +/- 0.2 fold) were not altered (ns). Finally chop and trb3 mRNA levels augmented drastically with H$_2$O$_2$ (17.9 +/- 4.8 and 34.4 +/- 6.3 fold, respectively, p<0.05). CONCLUSION: Hydrogen peroxide induces ER stress in C2C12 myotubes through at least the PERK pathway.