MIFEPRISTONE ENHANCES INSULIN SENSITIVITY THROUGH AMPK ACTIVATION IN L6 SKELETAL MUSCLE CELLS.

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The glucocorticoids are steroidal hormones responsible of maintain the body homeostasis, both in response to normal diurnal changes in metabolism and in response to stress. Long exposure to glucocorticoids produce several complications related to Cushing syndrome. These complications include hyperglycemia and insulin resistance, and one of the treatments for hyperglycemia in patients with Cushing syndrome is the FDA-approved drug mifepristone, a competitive glucocorticoid receptor antagonist. However, the mechanisms by which mifepristone produce their effect on glucose homeostasis is not completely understand. The proposal of this work is to determine mifepristone effect on mitochondrial metabolism and insulin signaling on L6 skeletal muscle cells.

**Material and methods:** We studied the effect of mifepristone on mitochondrial function and insulin signaling in L6 WT and L6 GLUT4-myc rat skeletal muscle cells. We evaluated the effect of mifepristone on mitochondrial function by assessing mitochondrial potential, oxygen consumption, ROS and ATP levels. To assess the impact of mifepristone on insulin signaling, we evaluated by immunoblotting phosphorylated and total forms of Akt, p70S6K and AMPK proteins; and the exposure of GLUT4-myc to the cell membrane surface and glucose uptake via the fluorescent substrate 2-NBDG. To determine the participation of AMPK on mifepristone effects in insulin signaling, we used an AMPK siRNA.

**Results:** Mifepristone reduced oxygen consumption, ROS and ATP levels, without changes in mitochondrial potential membrane. Mifepristone produce an increased on Akt and p70S6K phosphorylation in response to insulin. Also, mifepristone augmented basal exposure of GLUT4-myc to the cell membrane, and increased basal and insulin-stimulated 2-NBDG uptake. Moreover, increased AMPK phosphorylation occurs at 1, 3 and 6 h returning to basal levels at 24 h of mifepristone exposure. Finally, the use of AMPK siRNA shows that AMPK is necessary for mifepristone enhances insulin-dependent Akt phosphorylation.

**Conclusion:** Altogether, these results suggest that mifepristone enhances insulin sensitivity through AMPK activation in L6 skeletal muscle cells.

**Acknowledgements:** FONDECYT 11130285 (RT) and FONDAP 15130011 (RT) supported this work.

**Keywords:** Mifepristone, Insulin Sensitivity, AMPK.