

TREATMENT WITH OLEIC ACID AND A PPAR α AGONIST INCREASES FATTY ACID OXIDATION IN BEATING HUMAN INDUCIBLE PLURIPOTENT STEM CELL-DERIVED CARDIOMYOCYTES

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Aim:

Human inducible pluripotent stem cell-derived cardiomyocytes (hiSPC-CM) have an immature phenotype including a glycolytic metabolism. Here we aimed to mature the metabolic status of beating hiSPC-CM by targeting the PPAR- α pathway, which regulates the transcription of genes involved in fatty acid metabolism. We cultured hiPSC-CM with the fatty acid Oleic Acid (OA) with or without the PPAR- α agonist WY14643.

Methods:

hiPSCs cells were differentiated into beating hiPSC-CM by treatment with CHIR99021 followed by IWP4. Beating hiPSC-CM were treated with 400uM OA with or without 120uM WY14643 for 8 and 24 hours. Oxygen consumption was measured using a Clark-type oxygen electrode, glycolysis was measured by addition of 3H-glucose. Gene expression was measured using qPCR.

Results:

A significant increase in oxygen consumption and reserve respiratory capacity when respiring on fatty acid was observed in beating iPSC-CM after culture with OA + WY14643 for 24 hours compared with untreated and OA-treated hiPSC-CM. OA + WY14643 caused a significant increase in expression of carnitine palmitoyltransferase 1B, medium chain acyl-CoA dehydrogenase and pyruvate dehydrogenase kinase after 8 hours whilst expression of glucose transporters and phosphofructokinase decreased. Addition of OA, but not OA + WY14643, increased the rate of O₂ respiration on pyruvate and malate but not the reserve respiratory capacity. There was no change in the rate of glycolysis after treatment with OA +/- WY14643 for 24 hours.

Conclusion:

Treatment with OA and WY14643 for 24 hours increased fatty acid utilization in beating hiPSC-derived cardiomyocytes.

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