Inhibition of the Mitochondrial Calcium Uniporter Reduces Oxidative Phosphorylation in SGK1-Knockout VSMC Upon Diet-Induced Obesity
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Obesity is linked to vascular diseases such as atherosclerosis and coronary artery disease which is a major underlying cause of heart attacks. While the mechanism is not fully known, altering mitochondrial respiration which occurs through oxidative phosphorylation (OXPHOS) may influence the development of vascular disease during obesity. Our previous data with diet-induced obese (DIO) mice demonstrated that serum and glucocorticoid-inducible kinase 1 (SGK1), which regulates cell metabolism, was up-regulated in vascular smooth muscle cells (VSMC) from the aorta. Knocking out SGK1 in VSMCs (KO⁵⁴GK¹) was associated with higher OXPHOS and lower vascular disease relative to wildtype VSMCs (WT⁵⁴GK¹) during DIO. The mitochondrial calcium uniporter (MCU) permits calcium uptake into the mitochondrial matrix causing stimulation of OXPHOS thereby contributing to maintenance of cellular energy homeostasis. We hypothesized that OXPHOS stimulation in KO⁵⁴GK¹ VSMC may be due to enhanced activity of the MCU. To test this hypothesis, an extracellular oxygen consumption (EOC) assay which measures OXPHOS was used to examine the role of MCU-mediated mitochondrial Ca²⁺ uptake on basal and maximal OXPHOS activity in WT⁵⁴GK¹ and KO⁵⁴GK¹ VSMCs. Thus, WT⁵⁴GK¹ and KO⁵⁴GK¹ VSMCs from DIO mice were treated ± Ru360 (10μM), a MCU inhibitor and ± FCCP (2.5μM) to stimulate maximal OXPHOS. Consistent with previous data, KO⁵⁴GK¹ VSMCs had significantly higher basal and maximal EOC compared to WT⁵⁴GK¹ VSMCs. Remarkably, RU360 significantly decreased both basal and maximal EOC in KO⁵⁴GK¹ VCMCs. Conversely, there was no effect of RU360 on EOC in WT⁵⁴GK¹ VSMCs. These results suggest a disparity in MCU activity in KO⁵⁴GK¹ VSMCs. In conclusion, these findings implicate mitochondrial Ca²⁺ uptake in stimulation of OXPHOS in KO⁵⁴GK¹ VSMCs.