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Metformin Impacts Syncytiotrophoblast Mitochondrial Function in a Sexually Dimorphic Manner

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Keywords

placenta, mitochondria, metformin, diabetes, pregnancy

Abstract

Introduction

Placental mitochondrial respiration is impacted by obesity, type 2 gestational diabetes (A2GDM), and fetal sex. The mechanism of metformin, a GDM treatment, is unclear, but it may inhibit mitochondrial complex I, reducing mitochondrial respiration and ATP production. As previous studies examined the effect of metformin on cytotrophoblast but not syncytiotrophoblast (STB) we studied the effect on mitochondrial respiration in both male and female STB.

Methods

Placentas from lean (BMI<25), obese (>30), and A2GDM pregnancies (male or female fetus, n=4/group) were collected at term C-section. Isolated cytotrophoblasts were syncytialized (72 hrs) before 24 hr treatment with 0.01μM-30mM metformin. Mitochondrial respiration was assessed by Seahorse XF Mito Stress Test. Statistical analysis employed two-way ANOVA and Tukey post-hoc correction.

Results

STB of all groups showed a concentration-dependent decrease in basal respiration at 0.1-3mM metformin ($p<0.0001$ at 300μM). Maximal respiration decreased from 0.1-30mM metformin ($p<0.001$ at 1mM), but as the concentration response slope was significantly less than basal respiration ($p=0.006$), spare capacity (maximal - basal) was not significantly decreased until 3mM metformin. Female STBs of A2GDM pregnancies had significantly greater spare capacity vs. both lean ($p=0.006$) and obese women ($p<0.001$) at 100μM metformin. Oxygen consumption due to proton leak increased from 1-30μM metformin in male STB of A2GDM vs lean ($p=0.003$) and obese males ($p=0.05$), and vs females from A2GDM pregnancies ($p=0.01$). Male STB from lean pregnancies also exhibited proton leak compared to BMI-matched females ($p=0.03$ at 30μM).

Conclusion

Metformin concentrations near therapeutic circulating levels decreased STB basal and maximal mitochondria respiration. Spare capacity improved in female STB of A2GDM pregnancies at 100-300μM. However, metformin increases proton leak, uncoupling respiration, in STBs from male fetuses especially from A2GDM pregnancies.
Overall, metformin may differentially impact STB mitochondrial respiration, depending on concentration used: effects on male STB appear deleterious with some benefit for female STB.