

Role of Insulin Signaling in Prostaglandin Synthesis

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Background: This study explores the impact of the insulin/FOXO pathway on prostaglandin E2 (PGE2) synthesis in hypothalamic astrocytes. Previous research established insulin's role in activating FOXOs, leading to the expression of PTGS (COX-1, 2) and PTGES genes, ultimately driving PGE2 synthesis in astrocytes and influencing fertility. While earlier findings indicated insulin's ability to regulate PGE2 pathways in distinct astrocyte cell lines, questions remained about its specific effects on hypothalamic astrocytes.

Methods: To address this, astrocyte cell lines and primary astrocytes were isolated and treated with insulin or a control. Quantitative PCR and western blotting confirmed that 250nM of insulin induced Cox-2 expression within 30 minutes. Concerns about nonspecific signaling led to a decision to treat at 100nM for 6 hours. Transcriptomic analysis of RNAseq data revealed insulin's down-regulation of sterol and cholesterol biosynthesis pathway genes in male hypothalamic astrocytes. Kinome array analysis identified differentially phosphorylated kinases in the presence of insulin, with some sex-specific patterns.

Results: Notably, insulin phosphorylated AKT1, AR, P53, mTOR, RAF1, CDK1, GYS2, and MAPK10 in both sexes. MAPK1 showed male-specific phosphorylation, while MAPK3 and ISR2 displayed female-specific phosphorylation. In the presence of insulin, increased activity was observed in genes related to autophagy (more pronounced in males), various cancers, insulin resistance, type II diabetes, insulin signaling, FOXO signaling, and GnRH signaling and secretion (more prominent in females).

Conclusions: In conclusion, this study sheds light on how the insulin/FOXO pathway influences PGE2 synthesis in hypothalamic astrocytes. Insulin induces COX-2 expression and modulates pathways linked to sterol and cholesterol biosynthesis. Sex-specific phosphorylation patterns revealed by kinome analysis further contribute to our understanding of insulin and FOXO regulation in astrocytes, impacting PGE2 synthesis and associated pathways.