Role of Insulin Signaling in Prostaglandins Synthesis

Marziyeh Salehi Jahromi[1]*, Kathryn B. Smedlund[2], William G. Ryan[1], Ali Sajjad-Imami[1], Robert E. McCullumsmith[3], Jennifer W. Hill[2]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614
[2]Department of Physiology and Pharmacology, The University of Toledo, Toledo, OH 43614
[3]Department of Neurosciences, The University of Toledo, Toledo, OH 43614

*Corresponding author: marziyeh.jahromi@rockects.utoledo.edu

Keywords: Kinome, Insulin, Astrocyte, RNAseq, FoxO

Published: 22 November 2024

Background: Insulin signaling in astrocytes induces the expression of PTGS (COX-1, 2) and PTGES genes by activating FOXOs driving PGE2 synthesis and secretion to control fertility. Previous data show that insulin and FOXOs can regulate PGE2 pathways in two distinct astrocyte cell lines. These data also suggest that insulin increases PGE2 synthesis by activating FOXO-mediated transcription of COX-1,2, and/or PTGES2.

Objectives: We will investigate the regulatory effect of Insulin/FOXO pathway on PGE2 synthesis through FOXO in hypothalamic astrocytes.

Methods: Astrocyte cell lines and primary astrocytes were isolated, cultured, and treated with insulin or vehicle. Techniques including qPCR and western blotting techniques were used to measure signaling pathway changes related to prostaglandin production, prostaglandins were measured by ELISAs, and RNAseq analysis and Kinome array analysis were performed.

Results: Insulin treatment of Primary Mouse Astrocytes (PMA) and C8DA1 cells, confirmed by qPCR analysis for COX 1, 2 expressions, showed that 250nM of Insulin was effective as early as 30 minutes after treatment for inducing Cox-2 expression. Given previously published studies and concerns about nonspecific signaling at high doses, we chose to treat at 100nM for 6 hours. Our new DEG analysis of RNAseq raw data, obtained from a similar study, showed that Insulin down-regulates the expression of Sterol and Cholesterol Biosynthesis pathway genes in the male Hypothalamic Astrocytes. Kinome data analysis also showed differentially phosphorylated kinases in presence of Insulin when there is a almost no sex differentially phosphorylated kinases. AKT1, AR, P53, mTOR, RAF1, CDK1, GYS2 and MAPK10 are phosphorylated with Insulin in both sexes. MAPK1 is specifically phosphorylated in the males while MAPK3 and ISR2 are phosphorylated in females only of with Insulin in females only. Higher activity of genes involved in the Autophagy (higher in males), different types of cancers, Insulin resistance, Type II diabetes and Insulin signaling pathways, FoxO signaling, GnRH signaling and secretion in both sexes (higher in females) in presence of Insulin is shown.

Conclusion: This study investigates how the Insulin/FOXO pathway influences PGE2 synthesis in hypothalamic astrocytes. Insulin treatment induces COX-2 expression and affects gene pathways related to sterol and cholesterol biosynthesis. Kinome analysis reveals sex-specific phosphorylation patterns. Overall, the research enhances our understanding of insulin and FOXO regulation in astrocytes and their impact on PGE2 synthesis and associated pathways.

