Effect of TNF-alpha on Molecules Related to the Insulin Action in Endometrial Cells Exposed to Hyperandrogenic and Hyperinsulinic Conditions Characteristics of Polycystic Ovary Syndrome

Por: Orostica, L (Orostica, Lorena)\(^1\); Garcia, P (Garcia, Paula)\(^1\); Vera, C (Vera, Carolina)\(^1\); Garcia, V(Garcia, Victor)\(^2\); Romero, C (Romero, Carmen)\(^1,3\); Vega, M (Vega, Margarita)\(^1,3\)

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Abstract

Polycystic ovary syndrome (PCOS) affects not only ovarian functions but is also able to affect endometrium metabolism. Around 80% of women with PCOS are obese. High tumor necrosis factor (TNF)- production and low adiponectin levels are characteristics of obesity. Interestingly, endometrium from obese women with PCOS presents an insulin-resistance condition, high TNF- levels, and low adiponectin levels. However, TNF- effect on molecules associated with insulin action in endometrial cells remains unclear. Therefore, the objective of this work was to evaluate TNF- effect on expression of molecules associated with adiponectin (insulin sensitizing) and TNF- signaling pathways and on Glucose Transporter type 4 (GLUT-4) levels in human endometrial cells under the characteristic conditions of hyperandrogenic/hyperinsulinic (HA/HI) PCOS. Two human endometrial stromal cell lines (THESC/St-T1b) under HA/HI conditions were used to assay the effect of high TNF- concentration (100 ng/mL) on adiponectin, AdipoR1-AdipoR2 receptors, Adaptor protein phosphotyrosine interacting with PH domain and leucine zipper 1 (APPL1), Phospho-AMP-activated protein kinase T172 (p-AMPKT172), GLUT-4, Tumor necrosis factor receptor 1 (TNFR1)-Tumor necrosis factor receptor 2 (TNFR2) receptors protein levels, and nuclear factor B (NFB) nuclear content, by Western blot or immunocytochemistry. The NFB participation in TNF- effect on adiponectin expression was assayed using an NFB inhibitor (pyrrolidine dithiocarbamate). The TNF- increases the expression of molecules associated with its own signaling pathway (P < .05) and decreases the protein levels of adiponectin and its associated molecules (P < .05). Moreover, TNF- increases NFB nuclear content (P < .001), whereas with NFB inhibition the decrease in adiponectin content induced by TNF- was not observed. GLUT-4 levels were lower with TNF- treatment (P < .01). Thus, in human endometrial stromal cells,
high TNF-α levels negatively affect the insulin action through decreased adiponectin signaling and GLUT-4 protein. This could explain the failures observed in endometrial function of obese women with PCOS.

**Palabras clave**

**Palabras clave de autor:** endometrial cells; TNF-alpha; adiponectin; insulin; GLUT-4

**KeyWords Plus:** TUMOR-NECROSIS-FACTOR; INFLAMMATION-RELATED ADIPOKINES; GENE-EXPRESSION; GLUCOSE-UPTAKE; PCOS WOMEN; ADIPONECTIN; OBESITY; ADIPOCYTES; MECHANISMS; RESISTANCE

**Información del autor**

Dirección para petición de copias: Vega, M (autor para petición de copias)


Direcciones:

1. Univ Chile, Clin Hosp, Lab Endocrinol & Reprod Biol, Santiago, Chile
2. Univ Antofagasta, Fac Hlth Sci, Antofagasta, Chile
3. Univ Chile, Dept Obstet & Gynecol, Clin Hosp, Fac Med, Santiago, Chile

Direcciones de correo electrónico: mvega@hcuch.cl

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