Pro-Inflammatory Markers Negatively Regulate IRS1 in Endometrial Cells and Endometrium from Women with Obesity and PCOS

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Abstract

A pro-inflammatory environment is characteristic of obesity and polycystic ovary syndrome (PCOS). This environment through cytokines secretion negatively affects insulin action. Endometria from women with both conditions (obesity and PCOS) present high TNF-alpha level and altered insulin signaling. In addition, these patients present reproductive failures that could be associated to an abnormal endometrial function. Here, TNF-alpha and IL-6 effects on insulin signaling pathway were evaluated. Serum and endometrial IL-6, phospho-IRS1-S270 (inactive form) and phospho-IRS1-Y612 (active form) levels were evaluated in women with: Normal-Weight, Obesity and Obesity-PCOS. In endometrial cells under hyperandrogenic/hyperinsulinic conditions resembling PCOS, it was evaluated IL-6/TNF-alpha effects on phospho-IRS1-S270, phospho-IRS1-Y612, phospho-AKT-S473 levels, and S6K and JNK activation (IRS1-inactivating molecules). In obesity groups, diminution of IRS1-active form was observed, being more significantly in Obesity-PCOS; whereas, IRS1-inactive form increased in Obesity-PCOS. Serum and endometrial IL-6 were higher in Obesity-groups compared to Normal-Weight. In endometrial cells, TNF-alpha increases phospho-IRS1-S270, while IL-6 decreases phospho-IRS1-Y612. Importantly, TNF-alpha and IL-6 promote S6K and JNK activation; TNF-alpha increases and IL-6 decreases phospho-AKT-S473 levels. Thus, pro-inflammatory cytokines in endometrium could negatively influence insulin signaling by different mechanisms: TNF-alpha promotes activation of IRS1-inactivating kinases, whereas, IL-6 decreases IRS1 and AKT activation. Moreover, when obesity and PCOS are present the disruption of insulin signaling is aggravated. These effects could explain endometrial abnormal function and reproductive failures observed in women with obesity and PCOS.

Palabras clave

Palabras clave de autor:TNF-alpha; IL-6; IRS1; Obesity; PCOS

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