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Title

Altered Extracellular Regulated Kinase Signaling in skeletal muscle in women with Polycystic Ovary Syndrome

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Abstract

Introduction

Polycystic ovary syndrome is the most common gynaecological endocrine disorder in women of reproductive age. Peripheral insulin resistance is a feature of the disorder, leading to compensatory hyperinsulinaemia which has a suggested role in the pathogenesis. Previous studies examining the mechanism of insulin resistance have suggested altered phosphorylation of insulin receptor substrate (IRS), and in the phosphatidylinositol (PI) 3- Kinase activity implicating that the metabolic pathway is altered while other studies suggesting an alteration in the mitogen- activated Protein Kinase(MAP-Kinase) and Extracellular Regulated Kinase (ERK) signaling.

The aim of this study was to examine the insulin-signaling pathway in peripheral muscle to determine the possible site of insulin resistance in women with PCOS.

Methods

Nine women with polycystic ovary syndrome and seven weight-matched controls participated in the study. Each participant underwent an insulin tolerance test to establish insulin sensitivity (Bonora method). A muscle biopsy was taken from two separate sites from the Vastus lateralis at the fasted state and either at 20 minutes after bolus dose of insulin or if the bedside blood glucose estimation was ≥ 2.0 . The muscle biopsy was snap frozen in liquid nitrogen and kept at -80°C for later analysis. Baseline hormone profile was measured in both groups. Serial estimation of blood glucose, serum insulin levels were made at -15 , 0 and every 3 minutes thereafter following a bolus injection of soluble actrapid insulin 0.1 unit/ Kg body weight at 0 minutes. Protein extract was obtained from muscle biopsy followed by Western Blot analysis and Immunoprecipitation. Insulin signalling molecules IRS1, PKB, ERK 1/2 and MEK, both total and phosphorylated, in basal and insulin induced state were quantified. The change in the ratio of phosphorylated to total protein was compared in the two groups.

Results

The controls and PCOS groups were matched for BMI (23.8 v 29.2), waist hip ratio (0.86 v 0.87), but the controls were significantly older than PCOS (34 v 26 yrs, $p < 0.05$). Women with PCOS had significantly higher serum testosterone (1.7 v 3.4 nmol/L), lower SHBG (46 v 28.5), higher Free Androgen Index (2.65 v 11), and normal levels of TSH, Prolactin. The rate of fall of blood glucose between 3 - 15 minutes was the indicator for insulin sensitivity. Women with PCOS were insulin resistant compared to the control group with rate of fall of blood glucose being 4.03% /min (controls) and 3.33% / min (PCOS), $P = 0.04$. The interval between start of first biopsy and completion of second biopsy was 21 min in controls, and 25 min in PCOS ($P = 0.02$). Insulin increased the ratio (fold increase) of P-ERK to total ERK in all controls, but not in PCOS, where some subjects showed significant reduction (2.04 v 0.71 , $p = 0.02$). There was reduction in the ratio of P-MEK to total MEK in PCOS compared to controls though this did not reach statistical significance. This indicated a trend towards reduced activity of MEK upstream

of ERK in women with PCOS. We did not find any difference in the levels of basal and insulin induced ratio of phosphorylated to total IRS1 and PKB as previously reported. There was no correlation between BMI and alteration in ERK phosphorylation in women with PCOS, though there was reduction in activation of ERK in obese compared to non obese controls. There was no significant correlation of any measurements of the insulin signalling molecules- either basal or insulin induced to insulin sensitivity.

Conclusion

This study suggests that defect in the insulin signalling pathway in women with POCS appears to be upstream to ERK 1/2 in the presence of moderate degree of insulin resistance with subsequent reduction in ERK signalling and may implicate this pathway in the response of theca cells to hyperinsulinaemia, with resultant hyperandrogenaemia.

References

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