

Polycystic ovary syndrome — Studies of metabolic and ovarian disturbances and effects of physical exercise and electro-acupuncture

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien vid Göteborgs Universitet kommer att offentligt försvaras i hörsal Arvid Carlsson, Academicum, Medicinargatan 3, Göteborg, fredagen den 5 februari 2010, kl. 9:00

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Avhandlingen baseras på följande delarbeten:

- I **A New Rat Model Exhibiting Both Ovarian and Metabolic Characteristics of Polycystic Ovary Syndrome**
Mannerås L, Cajander S, Holmäng A, Seleskovic Z, Lystig T, Lönn M, and Stener-Victorin E
Endocrinology. 2007 148(8):3781-91
- II **Low Frequency Electro-Acupuncture and Physical Exercise Improve Metabolic Disturbances and Modulate Gene Expression in Adipose Tissue in Rats with Dihydrotestosterone Induced Polycystic Ovary Syndrome**
Mannerås L, Jonsdottir IH, Holmäng A, Lönn M, and Stener-Victorin E
Endocrinology. 2008 149(7):3559-68
- III **Acupuncture and Exercise Restore Adipose Tissue Expression of Sympathetic Markers and Improve Ovarian Morphology in Rats with Dihydrotestosterone-Induced PCOS**
Mannerås L, Cajander S, Lönn M, and Stener-Victorin E
Am J Physiol Regul Integr Comp Physiol. 2009 296(4):R1124-31
- IV **Adipose tissue characteristics, but not circulating sex steroids, are central factors in the pathogenesis of insulin resistance in women with polycystic ovary syndrome**
Mannerås-Holm L, Leonhardt H, Kullberg J, Jennische E, Odén A, Holm G, Hellström M, Lönn L, Olivecrona G, Stener-Victorin E, and Lönn M.
Manuscript



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ABSTRACT

Polycystic ovary syndrome (PCOS) is the most common endocrine abnormality in premenopausal women. The syndrome is characterized by hyperandrogenism, ovulatory dysfunction and polycystic ovarian (PCO) morphology. Metabolic disturbances, such as insulin resistance and obesity, are also associated with PCOS. Despite extensive research, the etiology and pathophysiological mechanisms of PCOS and related metabolic disturbances are largely unknown. The clinical management of PCOS is multifaceted but often unsatisfactory.

The main aims of this thesis were 1) to develop new rat PCOS models displaying ovarian and/or metabolic abnormalities, and to evaluate the effects of low-frequency (2 Hz) electro-acupuncture (EA) and physical exercise in the most complete of these models, and 2) to characterize the adipose tissue of women with PCOS (normal weight/overweight/obese) in terms of distribution, cellularity, lipid metabolism, release of certain adipokines and macrophage density, and to identify factors among these characteristics and serum sex steroids that are associated with insulin sensitivity in these women.

Female rats were continuously exposed either to the aromatase inhibitor letrozole or the nonaromatizable androgen dihydrotestosterone (DHT), starting before puberty, to induce a hyperandrogenic state. All rats exposed to letrozole became anovulatory and developed PCO morphology with structural changes strikingly similar to those in human PCOS, but without the metabolic abnormalities. Rats exposed to DHT displayed alterations in ovarian morphology and function, as well as metabolic abnormalities that included adiposity, enlarged adipocytes and insulin resistance in adulthood.

EA and exercise improved both insulin resistance and ovarian morphology in rats with DHT-induced PCOS. These results indicate that both interventions break, at least partly, the vicious circle of androgen excess, insulin resistance and ovarian dysfunction in PCOS. Both EA and exercise also partly restored altered adipose tissue gene expression related to insulin resistance, obesity, inflammation and high sympathetic activity, suggesting that exercise and EA may both influence regulation of adipose tissue metabolism/production and sympathetic activity. Interestingly, in contrast to exercise, EA exerted its beneficial effects without influencing adiposity or adipose tissue cellularity.

Compared to controls pair-matched by age and body mass index (BMI), women with PCOS had larger abdominal subcutaneous adipocytes, lower plasma adiponectin, and lower LPL activity (borderline significant). There were no differences in anthropometrical variables or in abdominal volumes of total, subcutaneous and visceral adipose tissue, as determined by MRI, between the groups. Women with PCOS also had lower insulin sensitivity, higher serum levels of testosterone, free testosterone and free estradiol as well as lower serum levels of sex hormone binding globulin. Multiple linear regression analysis revealed that adipocyte size, circulating adiponectin and waist circumference, but not circulating sex steroids, were the factors strongest associated with insulin sensitivity in women with PCOS.

In conclusion, androgens are likely to play a central role in the pathogenesis of PCOS. Our rat models of PCOS highlight the close relationship between androgen excess and the development of ovarian and/or metabolic disturbances typical of this syndrome. Women with PCOS display hyperandrogenemia, insulin resistance and adipose tissue abnormalities, although their adipose tissue distribution and abdominal volumes are indistinguishable from age/BMI-matched controls. The adipose tissue abnormalities in PCOS — enlarged adipocyte size and low circulating adiponectin — together with a large waistline, rather than the hyperandrogenemia, seem to be central factors in the development/maintenance of insulin resistance in these women. EA and exercise may both represent valuable non-pharmacological treatment alternatives in PCOS, with the potential to improve both ovarian dysfunction and metabolic disturbances.

Keywords: adipocyte size, adipose tissue, androgen excess, animal models, body composition, electro-acupuncture, insulin resistance, ovary, physical exercise, polycystic ovary syndrome