

Polycystic ovary syndrome

Effect of acupuncture on insulin resistance and neuroendocrine function

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien vid Göteborgs Universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, Göteborg, torsdagen den 28 februari 2013 kl. 9.00

av

Julia Johansson

Fakultetsopponent: Dorte Glintborg MD, PhD
Department of Endocrinology
Odense University Hospital, Denmark

Avhandlingen baseras på följande arbeten:

- I. **Hypothalamic neuroendocrine functions in rats with dihydrotestosterone-induced polycystic ovary syndrome: Effects of low-frequency electroacupuncture**
Feng Yi, [Julia Johansson](#), Ruijin Shao, Louise Mannerås, Julia Fernandez-Rodriguez, Håkan Billig, and Elisabet Stener-Victorin. *PLoS ONE* 2009, 4(8): e6638.
- II. **Acupuncture for ovulation induction in polycystic ovary syndrome: A randomized controlled trial**
[Julia Johansson](#), Leanne Redman, Paula P Veldhuis, Antonina Sazonova, Fernand Labrie, Göran Holm, Gudmundur Johannsson, and Elisabet Stener-Victorin. *Submitted*.
- III. **Intense electroacupuncture normalizes insulin sensitivity, increases muscle GLUT4 content, and improves lipid profile in a rat model of polycystic ovary syndrome**
[Julia Johansson](#), Feng Yi, Ruijin Shao, Malin Lönn, Håkan Billig, and Elisabet Stener-Victorin. *Am J Physiol Endocrinol Metab* 2010, 299:E551–E559
- IV. **Electrical vs manual acupuncture stimulation in a rat model of polycystic ovary syndrome: Different effects on muscle and fat tissue insulin signaling**
[Julia Johansson](#), Louise Mannerås-Holm, Ruijin Shao, AnneLiese Olsson, Malin Lönn, Håkan Billig, and Elisabet Stener-Victorin. *PLoS ONE* 2013, 8(1): e54357.

Göteborg 2013



UNIVERSITY OF GOTHENBURG

Polycystic ovary syndrome

Effect of acupuncture on insulin resistance and neuroendocrine function

Julia Johansson

Department of Physiology, Institute of Neuroscience and Physiology, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden

Abstract

Although polycystic ovary syndrome (PCOS) is the most common endocrine disorder amongst women in reproductive age the etiology and pathophysiology are poorly understood. PCOS is characterized by hyperandrogenism, polycystic ovaries and ovulatory dysfunction. It is also associated with metabolic disturbances, increased luteinizing hormone (LH) secretion and increased muscle nerve sympathetic activity. Acupuncture with combined electrical (EA) and manual needle stimulation has been demonstrated to improve menstrual frequencies and to reduce androgen and glucuronidated androgen metabolite levels in women with PCOS. In a dihydrotestosterone (DHT) induced rat PCOS model EA has been shown to improve insulin sensitivity, decrease markers of sympathetic activity in adipose tissue and to improve ovarian morphology.

The overall aims of this thesis were to evaluate the effect of acupuncture on ovulatory and neuroendocrine as well as metabolic dysfunction in women with PCOS and in rats with DHT-induced PCOS, and to search for potential molecular mechanisms mediating the effects. In the rat model we also sought to compare acupuncture with manual and electrical needle stimulation with regards to their efficacy and signaling mechanisms on glucose regulation.

EA 5 days per week during 4-5 weeks in DHT-induced PCOS rats restored estrous cyclicity and reduced elevated protein expression of hypothalamic gonadotropin releasing hormone (GnRH) and androgen receptor (AR). Immunohistochemistry also revealed a co-localization between the two, indicative of AR activation as a mediator of the effects. PCOS women were randomly allocated to either acupuncture with combined electrical and manual stimulation or attention control twice weekly for 10-13 wks. Ovulation frequency was higher in the acupuncture than in the control group, but was not accompanied by changes in LH or cortisol secretion patterns. Furthermore, most sex steroids; estrogens, androgens and androgen precursors and glucuronidated androgen metabolites decreased in the acupuncture group and differed from the control group. The effect on ovulatory function has now repeatedly been shown in both clinical and experimental studies. Here it appears to be related to regulation of sex steroids rather than gonadotropin secretion in women with PCOS although the rat data indicates a relation to normalization of hypothalamic aberrations after EA treatment. EA 5 days per week during 4-5 weeks normalized insulin sensitivity and increased low plasma membrane glucose transporter 4 content in skeletal muscle of DHT-induced PCOS rats while glucose tolerance was partly improved after manual stimulation. Manual stimulation primarily affected gene expression while electrical stimulation primarily affected protein expression, indicating different mechanisms of action. This suggests that treatment frequency and stimulation modality is of importance and that electrical stimulation of the needles is superior to manual stimulation although this needs to be investigated in clinic.

As shown in this thesis, acupuncture treatment elicits local and systemic effects which have the capacity to break the vicious circle of androgen excess, ovarian dysfunction and possibly reduced insulin sensitivity in PCOS. It may therefore represent an alternative or complement to standard pharmacological or surgical treatment.

Keywords: acupuncture, polycystic ovary syndrome insulin resistance, ovulation, neuroendocrine function, animal models.