Acupuncture and exercise restore adipose tissue expression of sympathetic markers and improve ovarian morphology in rats with dihydrotestosterone-induced PCOS

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Manneräs L, Cajander S, Lönn M, Stener-Victorin E. Acupuncture and exercise restore adipose tissue expression of sympathetic markers and improve ovarian morphology in rats with dihydrotestosterone-induced PCOS. Am J Physiol Regul Integr Comp Physiol 296: R1124–R1131, 2009. First published January 21, 2009; doi:10.1152/ajpregu.90947.2008.—Allergy to sympathetic nervous system of sympathetic nervous system, which innervates adipose and ovarian tissue, may play a role in polycystic ovary syndrome (PCOS). We hypothesize that electro-acupuncture (EA) and physical exercise reduce sympathetic activity by stimulating ergoreceptors and somatic afferent pathways in muscles. Here we investigated the effects of low-frequency EA and physical exercise on mRNA expression of sympathetic markers in adipose tissue and on ovarian morphology in female rats that received dihydrotestosterone (DHT) continuously, starting before puberty, to induce PCOS. At age 11 wk, rats with DHT-induced PCOS were randomly divided into three groups: PCOS, PCOS plus EA, and PCOS plus exercise. The latter two groups received 2-Hz EA (evoking muscle twitches) three times/week or had free access to a running wheel for 4–5 wk. In mesenteric adipose tissue, expression of β3-adrenergic receptor (ADRB3), nerve growth factor (NGF), and neuropeptide Y (NPY) mRNA was lower in untreated PCOS rats than in controls. Low-frequency EA and exercise downregulated mRNA expression of NGF and NPY, and EA also downregulated expression of ADRB3, compared with untreated rats with DHT-induced PCOS. EA and exercise improved ovarian morphology, as reflected in a higher proportion of healthy antral follicles and a thicker theca interna cell layer than in untreated PCOS rats. These findings support the theory that increased sympathetic activity contributes to the development and maintenance of PCOS and that the effects of EA and exercise may be mediated by modulation of sympathetic outflow to the adipose tissue and ovaries.

The autonomic nervous system has been suggested to contribute to polycystic ovary syndrome (PCOS) (15, 19, 20, 61). Features of PCOS and the related metabolic syndromes, such as hyperandrogenemia, hyperinsulinemia, insulin resistance, and abdominal obesity, are associated with disturbed activity of the sympathetic nervous system (13, 33). Women with PCOS have increased sympathetic and decreased parasympathetic components of heart rate variability, an indirect measure of cardiac autonomic control (61), and abnormal heart rate recovery, another measure of autonomic function (17). Furthermore, increased ovarian sympathetic nerve activity stimulates androgen secretion in rats (19, 47), and PCOS is associated with an increase in ovarian catecholaminergic nerve fibers (20, 48) and altered catecholamine metabolism (15, 49), suggesting increased sympathetic nervous system activity. Increased sympathetic nerve activity in the ovaries might contribute to PCOS by stimulating androgen secretion (19, 47). Ovarian surgeries reduce the amount of androgen-producing theca cells and the regulation of the hypothalamic-pituitary-ovarian axis is changed, which increases ovulatory response in women with PCOS (21). Additionally, ovarian surgeries may improve ovulatory dysfunction via disruption of ovarian sympathetic innervation.

Recently, we performed direct intra-neural recordings of sympathetic nerve activity in PCOS patients (58). This novel study showed that PCOS is associated with increased sympathetic nervous system activity, which correlated with the elevated testosterone levels that characterize this syndrome. Increased sympathetic outflow might explain the increased prevalence of vascular disease in women with PCOS and might contribute to its etiology.

Obesity and metabolic disturbances exacerbate many of the typical symptoms in women with PCOS and increase the risk of long-term health consequences. Adipose tissue participates in the integrative physiology of whole body glucose and fat metabolism and is innervated by the autonomic nervous system, mainly the sympathetic nervous system, which modulates its metabolic and endocrine functions (6). Alterations in sympathetic activity in adipose tissue can affect the metabolic and endocrine functions of other tissues by altering the secretion of fatty acids and adipokines. Indeed, in obese women with metabolic syndrome, circulatory concentrations and gene expression of nerve growth factor (NGF), a marker of sympathetic activity, are increased in subcutaneous adipose tissue (7). However, the expression of genes encoding sympathetic markers and the influence of therapy on those markers has not been studied in PCOS.

Since PCOS appears to be associated with increased sympathetic nerve activity, interventions thought to modulate sympathetic nerve activity, such as physical exercise (43) and low-frequency electro-acupuncture (EA) (39, 51), might be beneficial. In uncontrolled studies of women with well-defined PCOS and women with undefined ovulatory dysfunction, acu-
puncture exerted long-lasting beneficial effects on endocrine
delays, and anovulation without negative side effects (8,
40, 57). In overweight women with PCOS, exercise together
with other lifestyle modification decreases central fat and
increases insulin sensitivity and ovarioculum function (23, 27).
However, those studies were not focused on parameters related
to the autonomic nervous system or the mechanisms underlying
the effects of EA.

In rats with polycystic ovaries induced with estradiol valerate
(EV), we found that low-frequency (2 Hz) EA (3, 37,
53–56) and physical exercise (36) restored the ovarian expres-
sion of markers of sympathetic nervous system activity, con-
sistent with the notion that EA and exercise inhibit sympathetic
hyperactivity. In rats with PCOS induced with dihydrotestos-
terone (DHT), we showed that low-frequency EA and physical
exercise each reduced insulin resistance and the expression of
adipose tissue genes associated with insulin resistance, obesity,
and inflammation (35). EA did so without affecting adiposity
or adipose tissue cellularity.

Hyperandrogenism is the central feature of PCOS and may
be a key factor in the excessive sympathetic tone associated
with the syndrome. Our DHT-induced rat PCOS model de-
velopes obesity and display ovarian dysfunction, both of which
are associated with high sympathetic activity. Therefore, we
aimed to investigate the mRNA expression of the β3-adren-
ergic receptor (Adrb3), Ngn, NGF receptor (Ngfr), and neuropep-
tide Y (Npy), all markers of sympathetic nerve activity, and of
the androgen receptor (Ar) in adipose tissue in our rat model of
DHT-induced PCOS (34). We also assessed the effects of
low-frequency EA and physical exercise on the expression of
those genes and on ovarian morphology.

MATERIALS AND METHODS

Animals

Six Wistar dams, each with 8–9 female pups, were purchased from
Charles River (Frankfurt, Germany). Pups were raised with a lactating
dam until 21 days of age and were then housed four to five per cage
under controlled conditions (21–22°C, 55–65% humidity, 12:12-h
light-dark cycle). Rats were fed commercial chow containing 18.7%
protein, 4.7% fat, 63% carbohydrates, vitamins, minerals (B&K Uni-
versal, Sollentuna, Sweden), and tap water ad libitum. Animals were
cared for in accordance with the principles of the Guide to the Care
and Use of Experimental Animals (49a). The study was approved by
the Animal Ethics Committee of the University of Gothenburg.

Study Procedure

The study procedure has been described (35). In brief, at 21 days of
age, rats were randomly divided into two groups. The DHT-induced
PCOS rats (n = 36) were implanted subcutaneously in the neck with
90-day continuous-release pellets (Innovative Research of America,
Sarasota, FL) containing 7.5 mg of DHT (daily dose, 83 µg), which
induces metabolic disturbances and other characteristics of PCOS in
adulthood (34); controls (n = 13) received pellets containing 7.5 mg
of vehicle. Forty days later, to compensate for weight gain, an
additional pellet was implanted that released 3.5 mg of DHT or
placebo for 60 days (i.e., an additional daily dose of 58 µg).
A microchip (AVID, Norco, CA) with an identification number was
inserted along with the pellets. After 7 wk of DHT exposure, rats in
the PCOS group were randomly subdivided into three treatment
groups: PCOS (n = 12), PCOS plus exercise (n = 13), and PCOS plus
EA (n = 11). The treatments lasted 4–5 wk. The rats were weighed
weekly. The study was concluded after ~12 wk of DHT exposure,
when the rats were 15–16 wk of age.

EA. Low-frequency EA was administered to conscious rats every
second weekday for 4–5 wk (12–14 treatments). The treatment
procedure has been described in detail previously (35). Each treatment
lasted 15 min during the first week, 20 min during weeks 2–3, and
25 min during weeks 4–5. Acupuncture needles were inserted
bilaterally into the abdominal and hindlimb muscles, in somatic
segments corresponding to the innervation of the ovaries. The
intensity was adjusted to produce local muscle contractions and
varied from 0.8–1.3 mA.

Before needle insertion, rats were lightly anesthetized with 2% iso-
flurane (Isoba Vet; Schering-Plough, Stockholm, Sweden) in a 1:1
mixture of oxygen and air for 2–3 min. After needle insertion, the rats
were suspended in a fabric harness during EA treatment. To avoid
possible acute effects of EA, rats were not treated for 24 h before
the experiment was ended.

Physical exercise. Rats in the PCOS exercise group were placed
individually in cages with an exercise wheel and allowed to exercise
voluntarily for 4–5 wk. The exercise wheels were locked 24 h before
the experiment was ended to avoid possible acute effects of physical
exercise.

Three times per week, rats in the PCOS group and the PCOS
exercise group were anesthetized, suspended in a harness, and handled
in the same way as rats in the PCOS EA group but without needle
insertion or EA stimulation. All rats were conscious during the
handling/treatment procedure.

Vaginal smears. The stage of cyclicity was determined by mi-
rosopic analysis of the predominant cell type in vaginal smears
obtained daily from rats at 11 wk of age to the end of the experi-
m (38).

Tissue collection, RNA isolation and cDNA synthesis and real-
time RT-PCR. Rats were decapitated at 15–16 wk of age (i.e., after
4–5 wk of treatment and 11–12 wk after pellet implantation). The
mesenteric fat depot was dissected, snap frozen in liquid nitrogen,
and stored at −80°C for mRNA analyses. mRNA isolation and
real-time RT-PCR were performed as previously described in
detail by using a low-density array card (35). Primers and probes
for rat genes corresponding to the TaqMan Gene Expression
Assay numbers and GenBank accession numbers (Table 1). Gene expres-
sion values were calculated with the 2 −ΔΔCt method (31), where Ct is
cycle threshold. The ovaries were excised, fixed in neutral buffered
4% formaldehyde for 24 h, placed in 70% ethanol, dehydrated, and
embedded in paraffin.

Ovarian morphology. The ovaries were longitudinally and serially
sectioned at 4 µm; every 20th section (n = 5 per ovary) was mounted
on a glass slide, stained with hematoxylin and eosin, and analyzed
under a conventional birefringence microscope by two persons
blinded to the origin of the sections. The slides were scanned with
ScanScope (Aperio Technologies, Vista, CA) and analyzed with
ImageScope virtual microscopy software (Aperio Technologies). The
diameter of the ovaries in the section with the largest ovarian cross
section was measured with a calibrated scale tool in the virtual
microscope. Antral follicles, distinguished by an antrum within the
granulosa cell layers enclosing the oocyte, were counted by two
persons (to avoid duplicate counting) and classified as atretic or
healthy. Follicles were considered atretic if at least two pyknotic
granulosa cells were observed or if the oocyte showed obvious signs
of degeneration (22). The thickness of theca interna cell layer was
measured in the largest healthy and atretic antral follicles. Corpora
lutea were noted but not counted.

Statistical Analyses

All statistical evaluations were performed with SPSS software
(version 13.0; SPSS, Chicago, IL). Values are reported as means ±
SE. The Kruskal-Wallis test was used for comparisons of all groups,

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and if significant, a Mann-Whitney U-test was performed between individual groups. \( P < 0.05 \) was considered significant.

## RESULTS

### Exercise and EA Influence Ovarian Morphology

All control rats had a normal estrus cycle of 4 days. Rats in the PCOS group were acyclic, while those in the PCOS exercise and PCOS EA groups exhibited irregular cycles. Ovarian weight and area were lower in the PCOS group than in the controls, and neither variable was affected by exercise or low-frequency EA (Table 2).

Morphologically, ovaries from control rats exhibited follicles in various stages of development, ranging from primordial follicles to mature preovulatory follicles, as well as several corpora lutea, which often occurred after recent ovulations (Fig. 1, A–B). Some antral follicles contained pyknotic granulosa cells.

In rats with DHT-induced PCOS, small follicles in early development were observed, as were antral follicles with various degrees of atresia: some follicles had nuclear pyknosis in few cells, and others exhibited massive degeneration and granulosa cells in the antrum, as well as degenerated cells containing pyknotic nuclei scattered throughout the membrane granulosa (Fig. 1, C–D). Corpora lutea were absent in all PCOS rats. Although the number of antral follicles was similar in DHT-induced PCOS and control rats, DHT-induced PCOS rats had a higher proportion of atretic antral follicles (Fig. 2) in which the thickness of theca interna was increased (Table 2).

Rats in the PCOS exercise and PCOS EA groups had a lower proportion of atretic antral follicles (Fig. 2), and the theca interna cell layer in those follicles was thinner than in untreated DHT-induced PCOS rats (Table 2). However, both the PCOS exercise and PCOS EA rats had a significantly higher proportion of atretic antral follicles compared with controls (Fig. 2). In the PCOS EA group, fresh corpora lutea were observed in five of eleven rats (45%) (Fig. 1, E–F), indicating ovulation. In the PCOS exercise group, healthy follicles were observed, but no fresh corpora lutea (Fig. 1, G–H).

### PCOS Increases Gene Expression of Sympathetic Markers in Mesenteric Adipose Tissue

In mesenteric adipose tissue, expression of Adrb3, Ngfr, and Npy mRNA was higher in rats with DHT-induced PCOS than controls (Fig. 3). Expression of Ar and Ngfr mRNA did not differ in DHT-induced PCOS rats and controls (Fig. 3).

### EA and Physical Exercise Influence the Expression of Sympathetic Markers and AR in Mesenteric Adipose Tissue

Repeated low-frequency EA and physical exercise for 4–5 wk each lowered DHT-induced changes in the expression of Ngfr and Npy mRNA in mesenteric adipose tissue; EA also lowered the expression of Adrb3 and Ar mRNA (Fig. 3). Neither exercise nor EA influenced Ngfr mRNA expression (Fig. 3). Furthermore, the expression of selected genes after low-frequency EA and physical exercise were not significantly different from the corresponding level in control rats.

## DISCUSSION

Increased sympathetic activity may be an important etiological factor in PCOS (15, 17, 19, 20, 48, 49, 58, 61). Like the
metabolic syndrome, PCOS is characterized by insulin resistance and obesity, which are associated with enhanced activity of the sympathetic nervous system (28, 59). Recently, it was demonstrated that sympathetic activation is greater in subjects with central obesity, a feature of PCOS, than in those with peripheral obesity (18). These findings underscore the importance of evaluating new treatment strategies that attenuate sympathetic activity in patients with PCOS.

Using a rat model of DHT-induced PCOS, we show here that the expression of several markers of sympathetic activity is increased in mesenteric adipose tissue, a fat depot that affects metabolic status by releasing free fatty acids to the liver via the portal vein. This finding supports the notion that autonomic nervous system is involved in the pathogenesis of PCOS. Low-frequency EA and physical exercise each influenced ovarian morphology and downregulated the expression of several markers of sympathetic nervous activity in mesenteric adipose tissue, indicating that these interventions exert their effects by modulating sympathetic outflow to the adipose tissue and ovaries.

Fig. 1. A: ovary from a normal cycling control rat. B: high-power view shows a recently ovulated collapsed follicle with the apical rupture hole (broken arrow) closed by granulosa cells and perifollicular edema (thin arrow) typical of ovulation and (on the left) an antral follicle containing macrophages (thick arrow) and a trapped oocyte (long thick arrow). C: ovary from a rat with dihydrotestosterone (DHT)-induced polycystic ovary syndrome (PCOS) with small early atretic follicles (EAF) and antral follicles with various degrees of atresia. D: high-power view shows degenerating pyknotic granulosa cells in the antral part of the membrane granulosa in EAF. E: ovary from a rat in PCOS EA group with healthy follicles (HF), atretic follicles (AF), and fresh corpora lutea (FCL). F: high-power view shows FCL and a HF. G: ovary from a rat in the PCOS exercise group with HF, EAF, and old AF (arrows). H: high-power view shows a HF and an EAF.
Mechanisms Behind the Effects of Low-Frequency EA and Physical Exercise

Most likely, low-frequency EA and physical exercise exerted their effects in rats with DHT-induced PCOS by stimulating ergoreceptors and somatic afferents in the muscles, which results in modulation of spinal reflexes and central sympathetic outflow. Previously, we showed that low-frequency EA increases ovarian blood flow and that this effect is mediated as a reflex response via ovarian sympathetic nerves, which in turn is controlled via central nervous system pathways (50). Furthermore, reduction in central sympathetic activity, as reflected by a drop in blood pressure, after low-frequency electrical muscle stimulation is mediated by the release of \( \beta \)-endorphin (24, 25). Neurons that express proopiomelanocortin (the precursor of \( \beta \)-endorphin), NGF, NGFR, and neuropeptide Y (NPY) mRNA in mesenteric adipose tissue in control rats and in the 3 PCOS groups. The average cycle threshold (Ct) value for all genes was 28.6 ± 0.1 (range, 23.8–34.6).

Hypothetically, low-frequency EA and physical exercise could exert their effects in rats with DHT-induced PCOS by stimulating ergoreceptors and somatic afferents in the muscles, which results in modulation of spinal reflexes and central sympathetic outflow. Previously, we showed that low-frequency EA increases ovarian blood flow and that this effect is mediated as a reflex response via ovarian sympathetic nerves, which in turn is controlled via central nervous system pathways (50). Furthermore, reduction in central sympathetic activity, as reflected by a drop in blood pressure, after low-frequency electrical muscle stimulation is mediated by the release of \( \beta \)-endorphin (24, 25). Neurons that express proopiomelanocortin (the precursor of \( \alpha \)-MSH and \( \beta \)-endorphin) and other neuropeptides reside in the hypothalamic arcuate nucleus, a site for the regulation of metabolism and reproduction (9). Hypothetically, low-frequency EA and physical exercise could each modulate sympathetic outflow, metabolism, and release of gonadotropin-releasing hormone and luteinizing hormone (LH) through effects on \( \beta \)-endorphin and other neuropeptides (9, 51). Evidence that \( \beta \)-endorphin is involved in PCOS comes from recent trials in which naltrexone, a \( \mu \)-receptor antagonist, improved endocrine function (induced ovulation and decreases in LH, LH-to-follicle-stimulating hormone ratio, and testosterone) and metabolic function (decreases in body mass index and fasting serum insulin) in women with PCOS (1, 14).

Markers of Sympathetic Activity in Mesenteric Adipose Tissue. Effect of Treatment?

The autonomic nervous system has a distinct organization in different adipose tissue depots. The same set of neurons controls the various intra-abdominal adipose tissue depots, whereas subcutaneous adipose tissue located outside the abdominal compartment receives input from other autonomic neurons (45).

**NPY.** NPY, a phenotypic marker for sympathetic neurons, is colocalized and coreleased with norepinephrine at peripheral sites of action and is therefore considered a good indicator of sympathetic activity (42). In coculture with adipocytes, sympathetic neurons secrete increased amounts of NPY, suggesting cross talk between these two cell types (60). Adipose tissue and adipocytes both produce and secrete NPY (29), which is important in adipose tissue remodeling that results in abdominal obesity and metabolic syndrome (30). Consistent with these findings, mesenteric expression of Npy mRNA was higher in our DHT-induced rat PCOS model than in controls. Furthermore, in women with PCOS, circulating levels of NPY are elevated independently of body mass index (4). Both low-frequency EA and physical exercise resulted in pronounced downregulation of DHT-induced increase of in mesenteric Npy mRNA expression, indicating decreased sympathetic activity. Moreover, the mesenteric Npy expression after low-frequency EA and physical exercise were not significantly different from the corresponding level in control rats.

**NGF and NGFR.** The development and maintenance of sympathetic nerves are facilitated by the target-derived neurotrophin NGF and its low-affinity receptor (NGFR). NGF is secreted from adipocytes and can therefore be considered to be an adipokine (46), which may be involved in communication between adipocytes and sympathetic neurons. NGF expression is closely linked to inflammatory conditions, as TNF-\( \alpha \) stimulates NGF production by adipocyte (46). Overweight women and women with metabolic syndrome have high levels of circulating NGF (7), which are associated with insulin resistance, as well as increased levels of IL-6 and leptin. The high circulatory levels of NGF may reflect the increased levels of NGF mRNA in adipose tissue in obese women (7). NGF production in adipose tissue is also increased in genetic models of obesity in animals (44).
Exercise and EA Improve Ovarian Morphology

Ovarian morphology in DHT-induced PCOS rats has been extensively described elsewhere (34). In evaluating the effects of different treatment modalities, it is important to be aware that the rat is a multiorganum species. Therefore, the ovarian morphology of our DHT-induced rat PCOS model cannot be directly compared with human polycystic ovaries. For example, the decreased ovarian size, as well as increased proportion of atretic follicles, seen in this rat PCOS model, are not in line with human polycystic ovaries. Nevertheless, both exercise and low-frequency EA positively influenced ovarian morphology in rats with EV-induced polycystic ovaries (36, 54, 56).

In the present study, expression of Adrb3 mRNA in mesenteric adipose tissue was higher in rats with DHT-induced PCOS than in controls, supporting the notion that androgens enhance lipolytic activity in rodents (2). Low-frequency EA downregulated Adrb3 gene expression compared with untreated PCOS rats, and the Adrb3 expression after low-frequency EA was not different from the corresponding level in control rats. Exercise had no effect on Adrb3 gene expression. Lower Adrb3 expression in visceral adipose tissue might decrease lipolytic activity in this depot, a potential explanation for the increased insulin sensitivity induced by EA in our previous study (35).

AR. The presence of ARs in preadipocytes and adipocytes suggests that androgens contribute to the control of adipose development and regulation (10). The induction of PCOS in our rat model by continuous administration of DHT did not influence the expression of Ar mRNA in adipose tissue. However, after EA treatment, Ar gene expression in adipose tissue was lower than in untreated rats with DHT-induced PCOS, and did not differ from Ar gene expression in controls.

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Furthermore, the theca interna cell layer was thinner in both the PCOS EA and PCOS exercise groups than in PCOS rats. Since the theca interna is innervated by sympathetic neurons and is important in steroidogenesis (47), the reduced thickness might reflect inhibition of ovarian sympathetic neurons. Previously, we showed that low-frequency EA increases ovarian blood flow (50, 52). Transection of the ovarian sympathetic nerves eliminated this response and also reversed the changes in ovarian morphology induced by EV in rats with polycystic ovaries (5). These findings confirm the role of the sympathetic nervous system in the control of ovarian function. Further supporting the involvement of sympathetic nervous system in PCOS, women with the syndrome have significantly higher NGF levels in the follicular fluid than controls (16).

Perspectives and Significance

Previously, we found that women with PCOS had increased sympathetic nerve activity related to hormonal and metabolic features and that both testosterone and cholesterol were independent predictors of such activity, with testosterone having the stronger impact (60). It is not yet clear whether increased sympathetic activity is an etiologic factor in PCOS or a consequence of hyperandrogenism. However, our findings support the theory that increased sympathetic activity contributes to the development and maintenance of PCOS. Thus, therapies aimed at reducing sympathetic nerve activity might alleviate the signs and symptoms of PCOS.

Conclusion

In rats with DHT-induced PCOS, low-frequency EA and exercise each reduced the expression of genes encoding markers of sympathetic activity in adipose tissue and had beneficial effects on ovarian morphology, reflecting modulation of sympathetic outflow to the adipose tissue and ovaries.

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