Association of sympathetic nervous system activity with polycystic ovarian syndrome

W. Li, Y. Chen, L. Xu

Department of Obstetrics and Gynecology, West China Women's and Children's Hospital of Sichuan University, Chengdu (China)

Summary

Polycystic ovary syndrome (PCOS) is a disease with high prevalence which has various clinical manifestations and increased risk of long-term complications, such as dyslipidemia, diabetes, metabolic syndrome, and hormone related tumor. However, the etiology of PCOS is still unclear. Consequently, the effect of symptomatic treatment is not always satisfactory and the prognosis is also unpredictable. Currently, commonly psychological syndromes and imbalance of sympathetic neuroendocrine system have been found in PCOS population, and increasing evidence highlighted the hypothesis that characteristics of PCOS could be partially explained by the instability of the sympathetic nervous system (SNS). Furthermore, surgical intervention of animal trials in order to normalize SNS could improve symptoms of PCOS. This review attempted to clarify the relationship between SNS and PCOS development and then discuss the possible new therapies in PCOS treatment via regulating the SNS.

Key words: Sympathetic nervous system; Polycystic ovary syndrome; PCOS.

Introduction

Polycystic ovary syndrome (PCOS) patients are at high risk of many long-term complications, such as dyslipidemia, diabetes, metabolic syndrome, and hormone related tumor, as well as some adverse pregnancy outcomes [1-5]. However, the etiology of PCOS remains unresolved, which may partly due to the complex of manifestations that deeply conceal the natural pathogenesis of PCOS. Under the Rotterdam consensus criteria, PCOS influence amount of the general female population, and the prevalence is higher in women at reproductive age than female adolescents (10% vs 3%), which is in accordance with the great increasing tendency of age related sympathetic traffic in women [6-8]. Currently, various therapies for PCOS mainly include lifestyle change (exercise and dietary-specific interventions), medical (clomiphene citrate (CC), metformin, combined oral contraceptive (OCP), etc.) and surgical treatments (laparoscopic ovarian 'drilling' (LOD), ultrasound-guided transvaginal ovarian needle drilling, etc.) which aims at optimizing pregnancy outcomes, restoring regular menses, ameliorating hormonal and metabolic disturbances, while improving quality of life. Although positive effect of these interventions had been found in PCOS treatment compared with placebo, these improvements analyzed in systematic reviews are not optimistic, especially regarding the live birth rate, ovulation, and/or menstrual cyclicity [9-14]. As the prognosis of PCOS is limited by its unclear etiology, and in view of the high prevalence, it is rationale to explore the nature and following targeted therapy of PCOS.

The sympathetic nervous system (SNS) is responsible for regulating many homeostatic mechanisms in living organisms, and fibers from the SNS innervate tissues in almost every biological system. Previous researches including animal model and human showed that sympathetic nerve activity controls ovarian steroid biosynthesis, follicular development, and ovulation [15, 16], especially the superior ovarian nerve (suspensory ligament, SON), a kind of sympathetic fiber associated with the suspensory ligament, which predominately innervates the interstitial glands and follicles of the ovary [17]. Furthermore, increasing evidences highlight that all the vital signs of PCOS (i.e. oligo- and/or anovulation, clinical and/or biochemical signs of hyperadrenalism and polycystic ovaries found during early follicular phase, elevated serum luteinizing hormone/follicle-stimulating hormone (LH/FSH) ratio, levels of obesity, and insulin resistance (IR) [18] could be plausibly explained by the instability of the SNS in PCOS patients. The objective of this review is to summarize related studies about the relationship between SNS and PCOS development, in order to give insight to possible new therapies for PCOS treatment.

Influence of SNS on follicular development and apoptosis

As other organs, ovary is innervated by sympathetic fibers through neurotransmitter of catecholamines. Two main routes of receiving extrinsic sympathetic fibers have been detected: SON and ovarian plexus (ovarian plexus nerve, PN). SON has an obvious effect in regulating of interstitial glands function and follicular development, whereas the PN fibers has less norepinephrine (NE) synthesis and are mostly perivascular innervating [17, 19]. Over last years, evidences obtained underline the role of SON and its neurotransmitter in the ovarian phenomena.

Unilateral or bilateral section of SON were introduced to investigate the effect of sympathetic fibers on ovarian func-

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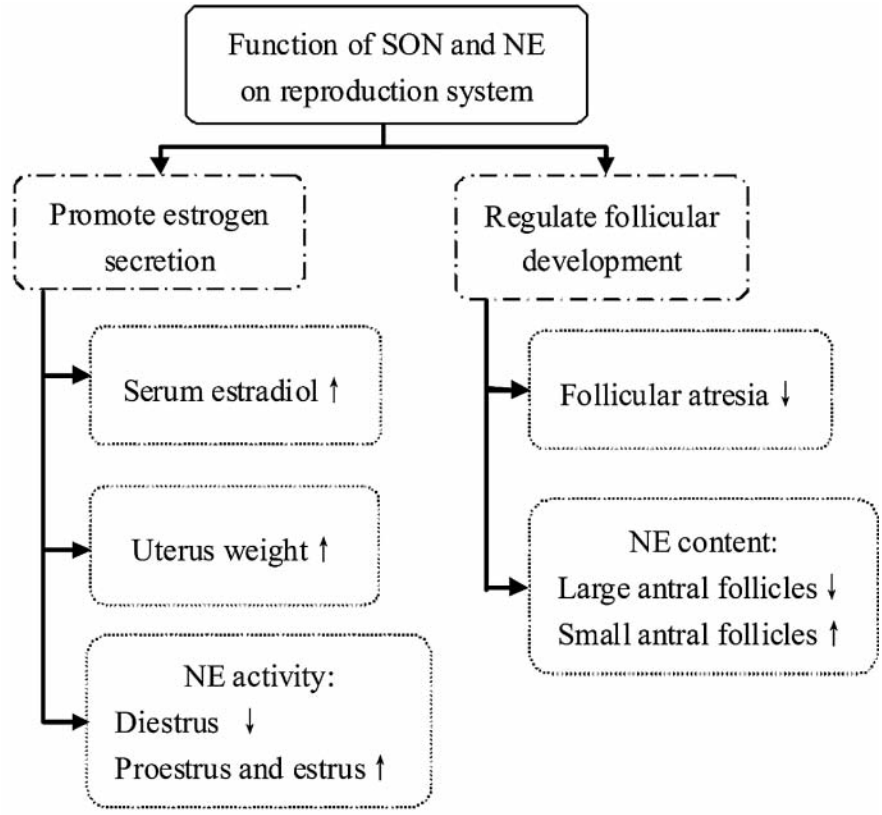

Figure 1. — Function of superior ovarian nerve (SON) and its main neurotransmitter norepinephrine (NE) on reproduction system. In animal model, (I) SON has the function of promoting estrogen secretion: SON can increase estradiol in serum and the weight of uterus which were verified by SON section; furthermore, the regularity of NE activity was accommodated to estrous cycle; (II) SON and its neurotransmitter can also regulate follicular development: in normal estrous cycle, NE content is lower in large follicles than small, and follicular atresia significantly increased after SON section, which all suggested that SON may have effect on regulating recuiment and selection.

tion. It has been observed that the percentage of follicular atresia significantly increased in both unilateral and bilateral SON sectioned rats. In addition, the raised number of atretic follicles was accompanied by decrease of serum estradiol in unilateral SON section and of uterus weight in bilateral section group [20]. NE, the main neurotransmitter released by SON fibers, has been found to have lower content in large antral follicles than in small ones [17], suggesting that SON may have a stimulatory effect on follicular development and over-activated SON may produce more small ovarian follicles. Furthermore, in unilateral SON section model, compensatory ovarian hypertrophy has been detected in innervated ovary [20, 21], and section in phase around ovulation would lead to increased ovulation rate [22]. From those studies, it could be deduced that SON might innervate ovarian function through catecholamines and then suppress ovulation, while overstimulation of SON might lead to oligo- and/or an-ovulation (Figure 1).

The NE release activity from ovarian sympathetic nerve changes throughout the estrous cycle. It increases during proestrus and estrus, and has lowest activity in diestrus phase in the rat (Figure 1). Moreover, these cycle-related alterations negatively correlated well with a ligand-induced expression of β-adrenergic receptors [23]. Therefore, activity of SON has provided vital feature in regulating follicular growth and secretory function of ovarian physiological process.

SNS related psychological change in PCOS patients

Psychological syndromes are commonly detected in PCOS patients. Compared with healthy women, they have higher depression and anxiety scores, and symptoms are particularly heavier in PCOS patients with obese or infertility [24-27]. On the other hand, the odds of having PCOS are positively associated with scores of depressive symptoms and the main symptoms of PCOS will in turn increase psychological syndromes [28, 29]. Furthermore, ovaries can receive neural signals and engender corresponding biological effects from sympathetic fibers, mostly carried by SON, which predominantly innervate secretory ovarian cells [17, 19], and interestingly, increase density of catecholaminergic fibers or have been detected by histofluorescence in human polycystic ovaries [30]. Moreover, their psychological distress or anxiety scores are obviously related to signs of androgen excess, such as hirsutism or acne [31, 32].

Further study showed that impaired psychological function not only influenced the quality of life but was also linked with some typical metabolism disorders in PCOS women, such as IR, obesity, and dyslipidemia [27]. A case-control study included PCOS and BMI-matched healthy women test relationship between metabolic disturbances and psychological symptoms containing depression, anxiety, and both (assessed by Beck Depression Inventory, State-Trait Anxiety Inventory, Hospital Anxiety and Depression Scale, and General Health Questionnaire, respec-

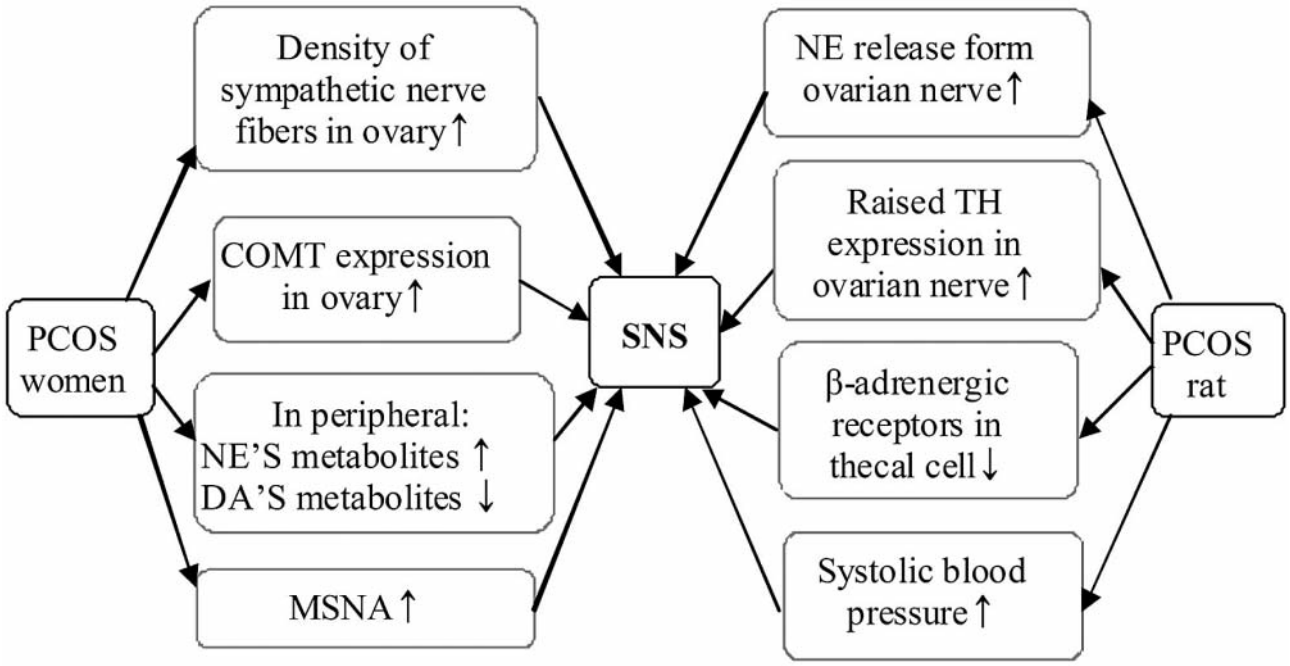

Figure 2. — Changes of sympathetic nerve system in women and animal with PCOS: (I) In women with PCOS, they have characteristics of increased density of sympathetic nerve fibers and expression of catechol-O-methyl transferase (COMT) in ovary, higher NE metabolites, lower DA metabolites and raised muscle vascular bed (MSNA); (II) In PCOS rat model, they have increased NE release and raised TH expression in ovarian nerve, down-regulated β-adrenergic receptors in thecal cell of ovary, and elevated systolic blood pressure. All these biologic changes belong to the sympathetic nerve system (SNS).

tively). It had been found that depression scores (test by depression, anxiety and reduced health-related quality of life, HRQOL) were significantly correlated with IR and lipid parameters. As it is clearly documented that PCOS has primary metabolic sequelae associated with IR and compensatory hyperinsulinemia, impaired psychological function may also be the central link in pathogenesis of the reproductive disturbances of PCOS [33].

Together these evidences, as anxiety and depression are intimately relate with dysregulated reactivity of the SNS [34-36], it is reasonable to deduce that the possibility of neuroendocrine disorders may also be involved in PCOS, and interaction between pathophysiological alternation and poor psychological function could participate in the control of PCOS development which will further aggravate clinical phenotypes.

Change of sympathetic system in ovary of PCOS

The over-activation of ovarian sympathetic nerve in ovary of PCOS is mainly supported by histofluorescence. It had been detected that polycystic ovaries from human patient with PCOS have an increased density of catecholaminergic nerve fibers compared with normal ovaries [37]. Many evidences based on animal model of PCOS induced by estradiol valerate (EV) also suggested the sympathetic hyperfunction in ovarian nerve: The release of NE from ovarian nerve terminals demonstrated significant time-dependent increase after EV injection accompanied by augmented NE content and incorporation of [3H]NE into ovarian tissue, and this phenomenon could be reversed by SON section [30, 38]. Contemporary, b-adrenergic receptors in thecal cell-interstitial tissue, which are directly innervated by sympathetic fibers, was distinctly down-regulated in the PCOS ovaries, and even lower during the estrous phase, phase with lowest β-adrenergic receptors concentration during normal estrous cycle [30] (Figure 2). These studies indicate that hyperfunction of SNS may play a role in the genesis of PCOS.

Catechol-O-methyltransferase (COMT) is the key enzyme which leads to inactivation of catecholamine neurotransmitters, such as dopamine, epinephrine, and NE. Inhibit this enzyme will lead increased granulosa cell (GC) proliferation and steroidogenesis [39]. Through immunohistochemistry, COMT expression had been clearly detected in cytoplasm of GC, theca cells (TC), and stromal cell layer in human ovary. In PCOS patients, COMT expression was dramatically increased in ovarian tissue (both in the follicular structures and ovarian stroma) in contrast with women who had proven fertility and normal ovulatory cycles [40]. Although whether the raised COMT expression in PCOS ovary is due to the over-release of catecholaminergic neurotransmitters from SON is still

unknown, these studies give us some clues: as GC is the main area for transforming testosterone into estrogen in ovary, the over expression of COMT in ovary tissue of PCOS may lead to decreased proliferation and steroidogenesis of GC, thus result in high testosterone in serum and follicular fluid and probably increase of serum metabolites of NE as well. In accordance, PCOS rat also manifest overactivated sympathetic function demonstrated by elevated mean systolic blood pressure (MSAP) and expression of tyrosine hydroxylase (TH), a marker for the biosynthesis of NE, in celiac ganglion projecting to the ovary [41, 42] (Figure 2).

Alternation of sympathetic neurotransmitter in PCOS

Recently, abnormal metabolism of several neuroendocrine factors related to SNS had been reported in PCOS patients, including dopamine (DA) and its metabolites homovanillic acid (HVA), and dihydroxy-phenyl acetic acid (DOPAC), norepinephrine (NE), and its metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG), NE's primary presynaptic metabolite named dehydroxy-phenylglyco (DHPG), vanillylmandelic acid (end-stage metabolite of epinephrine and NE, VMA), COMT, and its substrate 2-hydroxyestrogen.

Examination of catecholaminergic transmitters in peripheral organ systems also verified the abnormal activity of sympathetic system in PCOS patients. In the study with women with PCOS or hypothalamic-pituitary dysfunction, levels of NE's metabolite MHPG in urine were much higher in PCOS group compared with hypothalamic-pituitary dysfunction women and control group [25]. Considered the impact of menstrual cycle on catecholamine metabolism, another similar study tested the catecholaminergic nerve systems activity according to the different phases of menstrual cycles. It had reported that although urinary DA, NA, and adrenaline had no significant difference between PCOS and control, total concentrations of NE's metabolite MHPG remained higher in both early follicular and preovulatory phase and MHPG/VMA ratio were significantly higher in early follicular phase alone. In addition, the variation of those metabolites could not be modified by cabidopa administration, which inhibits DA synthesis mainly in peripheral of organic systems [26]. In another study compared infertility women with PCOS to those without PCOS, DA's metabolites HVA in serum was also detected significantly lower in PCOS group [24] (Figure 2).

With regards to adolescents aged 14 to 20, alternation in sympathetic neurotransmitters detected in early follicular phase were similar to PCOS women in reproductive age [43]. The concentrations of HVA and DOPAC in urine, metabolites of DA, had also been found to be significantly lower in early follicular phase in PCOS patients compared with control subjects, despite no such significance had been found in preovulation. Although NE's metabolite DHPG in plasma and urine was lower in PCOS patients than regular cycling control throughout the study, free dihydroxyphenylalanine (Dopa), A, NA, and total DA were similar in two groups. On the other hand, PCOS patients had higher urinary excretion of normetanephrine (NMN), NE's ultimate metabolite generated by catalysis of COMT (Figure 2).

Another way to evaluate global sympathetic nerve activity is to directly record sympathetic nerve activity of muscle vascular bed (MSNA) in quiescent condition which correlates well with global examination. MSNA measured in early follicular phase (during 1~7 days in menstrual cycles) in subjects of reproductive age, was dramatically increased in PCOS group and positively correlated with the level of serum testosterone and cholesterol [44]. As early follicular phase well reflects basal situation of hormones, results above suggested that altered peripheral catecholaminergic metabolism including NA excess and DA deficiency was one of the features in PCOS patients. This provided insight that PCOS might be associated with neuroendocrine disturbance.

Relationship between SNS and reproductive endocrinology in PCOS

Although high LH/FSH ratio and elevated LH levels are inconstant symptoms and has little use in PCOS diagnosis, they still influence approximately 45% of PCOS women [45]. Further analysis revealed that higher level of LH might be related to amenorrhea and increased adrenal androgenic activity [45, 46]. Abnormal catecholaminergic neurotransmitters founded in previous were related to aberrant reproductive endocrine in PCOS patient, especial elevated levels of NE's metabolite MHPG which maybe associated with some of the hormonal derangements. It was reported that there were positive correlations between MHPG and LH, LH and T, and levels of MHPG and DHEA-S, the precursor molecule of testosterone which positively correlates with acne in PCOS [25, 47]. Generally, the preovulatory LH surge appeared soon after the time when hypothalamic NE secretion was elevated, concomitant with increased expression of TH mRNA in noradrenergic neurons, LH releasing hormone (LHRH) level, and also LH secretion, whereas complete removal of adrenergic input to ovary through ovarian neurectomy could dramatically decrease concentrations of LHRH, expression of beta-adrenergic receptors and LHRH-binding activity [48-51]. For the amplitude of pulsatile LH is regulated by LHRH, it is possible that imbalance of sympathetic neuroregulation of hypothalamo-hypophyseal system will indirectly aggravate the disorders of PCOS resulting from high LH level. Moreover, increased the level of NE's metabolites and decreased level of DA's metabolites suggested high NE and low DA tone may contribute to inappropriate hypothalamic secretion of LH in PCOS. In accordance, administration of DA and its agonist caused a decrease of LH levels in PCOS patients [52, 53], and PCOS patients of central genesis had been detected with excess of serum LH that was conditioned by the falling influence of dopaminergic system [54]. As NE acts as an vital activator in

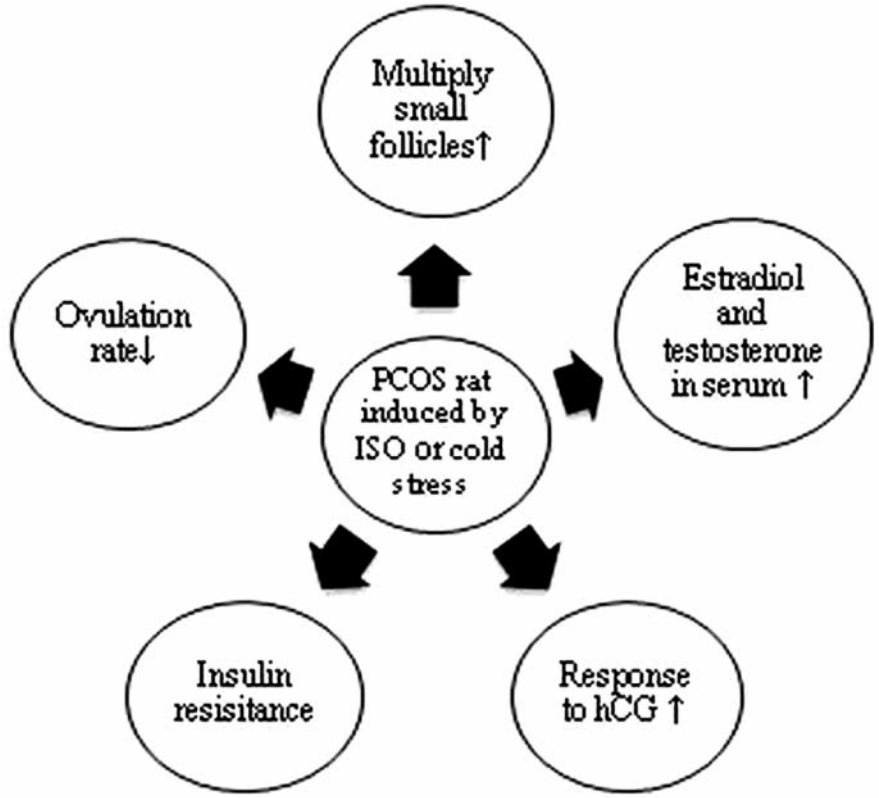

Figure 3. — Characteristic of PCOS rat induced by stimulating sympathetic nerve system: to stimulate sympathetic system by chronical cold stress or by agitating beta-adrenergic receptor through isoproterenol (ISO) will lead PCOS-like changes in rats, including multiply small follicles, decreased ovulation rate, over response to hCG, elevated serum estradiol, and testosterone in serum and insulin resistance.

LH release indirectly through stimulating GnRH secretion [55], while the dopamine system acts as inhibitor in GnRH production [52], these give further credence that inappropriate tone of catecholaminergic neurotransmitter may influence PCOS development through central mechanisms and further arouse aberrant secretion of LH.

Hyperandrogenism is another well-known feature of PCOS generated by multiple antral follicles. Physiologically, the secretion of androgen is under the regulation of hypothalamic-pituitary-adrenal/gonadal (HPA) axis which is dominated by sympathetic nervous system. In PCOS patients, the mean ratio of catecholamine metabolites DOPAC, a marker of central dopaminergic activity, against norepinephrine metabolites DOPEG (dihydroxyphenyl ethylene glycol), one of the indicator of adrenergic activity, was significantly higher than control group, and DOPEG or the DOPEG/DOPAC ratio was also significantly correlated to free testosterone. It is indicated that altered catecholamine activity in PCOS women is not only related to psychological disorder but also correlated with hyperandrogenemic status [56]. In animal mode of PCOS induced by isoproterenol (ISO), a beta-adrenergic receptor agonist, the ovaries obtained characterized PCO change (increased number of pre-cystic and cystic ovarian follicles) and increased androgen secretory activity of ovary accompanied by increased plasma LH levels (Figure 3). Moreover, most of these phenomena could be reversed by propranolol (PROP), a beta-adrenergic receptor antagonist. In summary, epinephrine-like effect stimulated by ISO could produce PCOS related symptoms containing increased LH plasma levels, PCO change of ovaries, and enhanced androgen ovarian secretory on animal model, which strongly suggested that beta-adrenergic agitation maybe definitive part of PCOS development [15].

Relationship among sympathetic system, IR, and obesity in PCOS

IR influences about 50% to 70% of PCOS women and appears to underlie many endocrine features of this disease through its secondary hyperinsulinemia [57]. Currently, IR and central obesity are considered to be the core of pathophysiological changes of PCOS [33].

Compared with obese control, the obese women with PCOS exhibited blunted response of noradrenaline to insulin induced hypoglycaemia. In addition, the response of noradrenaline to hypoglycaemia negatively correlated with fasting insulin levels in PCOS women (pooled obese and non-obese) but not in control group [58]. The lower responding activity to insulin indicated that there could be potential IR in SNS of PCOS women. Further study on rat examined the relationship among sympathetic system, IR and PCOS. It has been reported that cold stress induction, which could trigger increased sympathetic nerve activity to rat, promotes typical polycystic ovary morphology, low ovu-

lation, thickened theca cell (hyperthecosis) of antral follicles, elevated testosterone, and estrogen in estrus, and also ovarian hyperstimulation through hCG treatment in vitro experiment [59] (Figure 3). Besides, these PCOS like changes were accompanied by local sympathetic and selective ovarian resistance to insulin [16, 59] (Figure 3). All pathophysiological signs mentioned above are the typical changes in PCOS women. It was manifested by low response of NE release to insulin in ovary, especially in theca-interstitial cells (TC) compared with granulosa cells (GC) [16] (Figure 2).

Until now, the relationship between sympathetic system and IR is still a chicken-and-egg riddle. Insulin demonstrates positive effect on enhancing sympathetic activity in central nervous system by suppress inhibitory pathway of sympathetic outflow between the hypothalamus and brainstem sympathetic centers [7]. Persistent IR in peripheral organic systems is associated with increased sympathetic activity in women with history of pre-eclampsia [7]. On the other hand, many evidences have indicated that epinephrine overflow from sympathetic system can reduce the insulin-mediated glucose uptake and further produce IR [60, 61], and β-adrenergic receptor may play more important role than α-receptor in this process [62-64]. Thus, these two factors form an vicious circle and further pay impact on PCOS development, and it is rational to be speculated that the symptoms will be improved if any of them is inhibited.

Except IR, the aberrant relationship between SNS and adipocyte also occurs in PCOS. Current evidences demonstrated that pronounced truncal-abdominal body fat distribution (waist hip ratio, WHR) inversely correlated with basal levels of noradrenaline in obese women with or without PCOS [58]. To understand the role of SNS in PCOS obesity, a study focusing on subcutaneous fat cells has been explored that adipocytes in non-obese PCOS patients are about 25% larger and had 40% reduced noradrenaline-induced lipolysis compared with matched, healthy control. These can be probably explained by significantly decreased protein content and sensitivity of β2-adrenergic receptors in adipocyte [65]. According to the evidence list above, the detected morphological change (enlarged fat cell size) and functional alternations (catecholamine resistance of lipolysis) in adipocyte of PCOS may further promote later development of obesity in PCOS.

Effect of SNS-related surgery on PCOS

At present, the therapies for PCOS is symptomatic treatment, such as medicine for descending androgen, inducing ovulation, promoting follicular maturation regulating menstrual cycle or ameliorating IR. However none of them can resolve all the symptoms and metabolic abnormalities alone. As the sympathetic systems may be the pivotal point in the development of PCOS pathophysiological process (Figure 2), the authors assumed that to change the abnormal status of sympathetic systems in PCOS may be a suspected effective therapy. Based on published evidences, two obese PCOS patients with high blood pressure had undergone renal denervation with the credence that renal nerve ablation can reduce sympathetic spillover and further improve IR and hypertension [66]. After three-month follow-up, over-activated of SNS demonstrated by elevated NE outflow and muscle sympathetic nerve activity in those women was reduced. Contemporarily, down-regulated sympathetic activity is associated with substantial improvement in insulin sensitivity assessed by euglycemic hyperinsulinemic clamp in the absence of weight changes. Also in PCOS patients undergoing bilateral ovarian wedge resection, when compromising the hilum (the point of sympathetic nerves entry into the ovary), the prognosis has been shown efficacious especially in women with standard hormonal therapy resistance [30].

In animal model, intervention focus on regulating SNS also had demonstrated a positive effect on PCOS symptoms. After unilateral or bilateral sectioning of SON, PCOS rats induced by EV presented regular estrous cycles and recovered serum levels of testosterone and estradiol. The unilateral sectioning of the SON in these EV-induced PCOS rats resulted in higher spontaneous ovulation rates and less number of ova shed in the denervated ovary, while did not affect ovulation in wild type, which suggested that the denervated ovary recovered from PCO status since transection of SON [38, 67]. In addition, elevated estrogen, androgens, and testosterone were all significantly relieved after SON bilateral section [38, 67], and the SON transection also reversed elevated NE concentration and caused up-regulation of beta-adrenoreceptors of innervated ovary in EV induced PCOS rats. In accordance, to agitate beta-adrenergic receptor by ISO or to stimulate sympathetic system by chronical cold stress will lead PCOS-like changes in rats [15, 16, 38, 59] (Figure 3). Furthermore, over-secretion of androgen and estradiol from ovary stimulated by both ISO and HCG could be reversed by selective SON transection in EV-treated PCOS rat [38]. As PCOS is the risk factor of ovarian hyperstimulation syndrome (OHSS), it could be speculated that the over-function of β-adrenergic tone might play an important role in pathophysiological process in PCOS. In PCOS rats induced by cold stress, to down-regulate their sympathetic activity through bilateral electrolytic lesions in locus coeruleus (LC), the noradrenergic nucleus which regulate the hypothalamus-pituitary-adrenal axis and connect to the ovarian sympathetic pathway, can also improve PCO status, including reduced numbers of cystic follicles and small follicles, improvement of ovulation, and also decrease of serum estradiol and testosterone [59].

To summarize, these evidences suggest that (1) overactive function of SNS and related imbalance of catecholamine homeostasis have an crucial role in the PCOS development, (2) SNS may directly regulate ovarian functions and thus involve in PCOS genesis, (3) alternations in ovarian cycles, estrogen, androgens, and testosterone in PCOS rat may be controlled by neural information arriving

to the ovary through SON. Thus, it seems possible that the imbalance of SNS plays an important part in PCOS development through influencing ovarian function through both central and peripheral pathways. To resolve the overacted sympathetic activity either the central or peripheral nervous system will normalize ovarian cyclicity, ovulatory capacity, and hormone level in PCOS. Evidence supported by SON section modules of PCO rat reveal an optimistic future in developing new treatment. Otherwise, further studies are still needed for the efficacy and safety before widely used.

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Address reprint requests to:
L. XU, M.D.
Department of Obstetrics and Gynecology
West China Women's and Children's Hospital
of Sichuan University, Chengdu, Sichuan (China)
e-mail: liangzxu@126.com