The Scientific Connotation of Yin-Yang Interdependence and Interpromotion: A Perspective from the Synthesis and Function of Estrogen

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Abstract

The Yin-Yang theory is the fundamental principle in traditional Chinese medicine (TCM). In this study, we investigate the scientific connotations of Yin-Yang interdependence and interpromotion by using the estrogen synthesis pathway and its function as a biological model. Yin-Yang interdependence refers to mutual reliance for existence, which is illustrated by cholesterol (Yin, the substantive raw material) and key enzyme activity (Yang, functional catalysis) in estrogen synthesis, where no reaction occurs without either. Yin-Yang interpromotion means synergistic support, such as androgens (Yin, substance) promoting estrogen synthesis via aromatase (ARO1, Yang, enzyme activity), maintaining estrogen homeostasis. Estrogen, a steroid hormone, is synthesized from cholesterol through a sequential conversion process (cholesterol → pregnenolone → progestogen/androgen → estrogen) occurring in the ovaries, placenta, and peripheral tissues, and it interacts bidirectionally with cholesterol, pregnenolone, progestogen, and androgen. The endogenous E2 remains at a relatively high level in *ARO1*-knockout homozygous female mice, hinting at an alternative E2 pathway. This study verifies Yin-Yang theory with modern biology, laying a foundation for future research on the alternative estrogen pathway and TCM-informed therapeutic targets for estrogen-related processes.

Keywords: Yin; Yang; estrogen; aromatase; cholesterol

Introduction

The interdependence and interpromotion of Yin and Yang is one of the core contents of the Yin-Yang theory in traditional Chinese medicine (TCM)[1,2]. It serves as an important theoretical basis for explaining human physiological homeostasis and pathological changes, as well as for guiding clinical diagnosis and treatment. Its scientific connotation is being gradually clarified and verified through modern biomedical research[3–5]. The core connotation can be summarized as: Yin and Yang are interdependent, interpromoting, and inseparable. It is

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elaborated in detail from the following two dimensions:

Firstly, Yin-Yang interdependence means mutual dependence as a precondition. The core definition of interdependence means that Yin and Yang rely on each other for their existence—without Yin, there is no Yang, and vice versa. They are not isolated opposites but two interdependent aspects composing an organic unity. *Huangdi Neijing·Suwen·Yinyang Yingxiang Dalun* [黄帝内经·素问·阴阳应象大论] proposes that Yin resides internally, acting as the guardian of Yang; Yang remains externally, serving as the messenger of Yin [阴居内，是阳的守护者；阳居外，是阴的信使]. This vividly illustrates that Yin is the material foundation of Yang (internal guardian), while Yang is the functional manifestation of Yin (external motive force). Traditionally, the substantive basis of the human body (such as zang-fu organs) categorizes as Yin, and physiological functions (such as metabolism and zang-fu activities) categorizes as Yang. Without the substantive basis (Yin), functional activities (Yang) cannot be generated; without functional activities (Yang), the material basis cannot be synthesized or maintained. In estrogen synthesis, raw materials such as cholesterol (substantive basis, Yin) and the catalytic activity of key enzymes (functional activities, Yang) are mutually dependent[6]. Without raw materials, enzymatic reactions cannot be initiated; without enzymatic activity, raw materials cannot be converted into bioactive estrogen—this perfectly embodies the interdependence of Yin and Yang.

Secondly, Yin-Yang interpromotion means mutual synergy and promotion in function. The core definition of interpromotion means that Yin and Yang further promote and support each other base on the interdependence, jointly completing the physiological functions of the body and maintaining dynamic balance[7]. *Huangdi Neijing·Suwen·Shengqi Tongtian Lun* [黄帝内经·素问·圣气通天论] proposes that Yang transforms qi, and Yin transforms substance [阳化气，阴化物]. This indicates that Yang promotes substantive transformation and metabolism (qi transformation, such as various enzymes), while Yin is responsible for the formation of endogenous metabolites (substance formation, such as metabolites). In the regulatory network of estrogen synthesis, androgens (as a substance, categorized as Yin) serve as the precursor of estrogen[8,9]. They promote the synthesis of endogenous estrogen through aromatase (ARO1) activity (as an enzyme, categorized as Yang), thereby exerting a synergistic effect. Their interpromotion ensures the precise homeostasis of estrogen synthesis.

The synthetic pathway of estrogen

As a steroid hormone, the core raw material for estrogen synthesis is cholesterol[6,10,11]. Its main synthesis sites include the ovaries (in reproductive-age women), the placenta (in pregnancy women), and peripheral tissues such as the adipose tissue, the liver, and the mammary glands (in perimenopausal women). Estrogen synthesis follows a stepwise transformation process: cholesterol → pregnenolone → progestogen/androgen → estrogen, where the catalytic action of key enzymes constitutes the core rate-limiting step[10,12]. Briefly, the process mainly involves the conversion of cholesterol to pregnenolone, pregnenolone to testosterone, testosterone to estrogen (including estrone, estradiol, and estriol), as well as their metabolism and activation (Fig. 1). Therefore, at any stage, cholesterol and the following pregnenolone serve as the raw materials for estrogen, and the same is true for to androgens and progestogens, which reflects the characteristic of the interdependence of Yin and Yang. In other words, sufficient but not abnormally elevated cholesterol serves as a guarantee for progestogens, androgens, and estrogen.

Estrogen and cholesterol

As mentioned earlier, cholesterol is the common precursor molecule for all steroid hormones, including estrogen, while estrogen also exerts multifaceted effects on the metabolism and transport of cholesterol. On the one hand, estrogen exerts its effects on cholesterol metabolism mainly by regulating the synthesis, transformation, and clearance of lipoproteins. Estrogen exerts its effects by regulating plasma lipoprotein levels, thereby affecting the concentrations of LDL-C, HDL-C, and triglycerides, and it exhibits synergistic or antagonistic effects with progestogens[13]. On the other hand, estrogen may influence the intracellular transport of cholesterol through multiple pathways, thereby affecting its availability as a steroid precursor[11]. At the transport level, although estrogen does not explicitly directly regulate the transport of cholesterol to the inner mitochondrial membrane (the rate-limiting step of steroid synthesis), it can ensure the

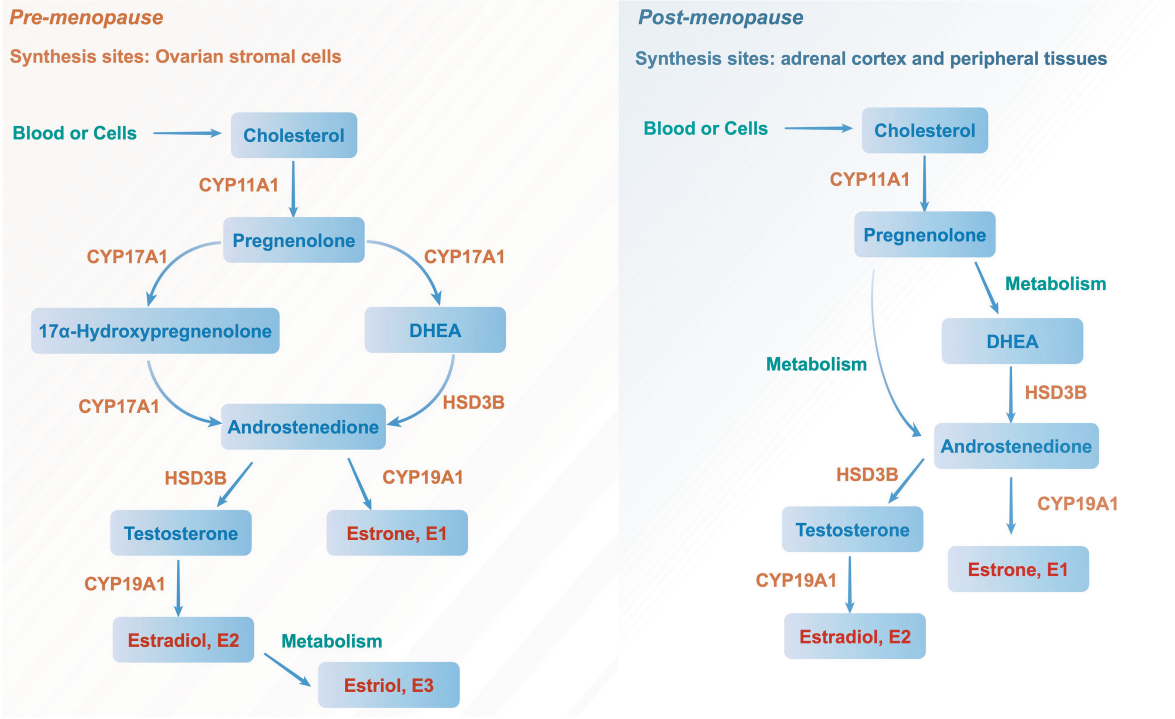

Figure 1: Estrogen synthesis pathway. DHEA: dehydroepiandrosterone.

substrate supply for its own synthesis through feedback regulation. Additionally, in tissues such as the hippocampus, it drives local cholesterol metabolism to meet the demand for local estrogen[14]. Furthermore, estrogen exerts a protective effect on the cardiovascular system by optimizing the lipid profile (increasing HDL-C and decreasing LDL-C), but this effect is influenced by the type and dosage of estrogen, as well as its combination with progestogens[15,16]. Previously, we also observed that estrogen deficiency induces total cholesterol (TC) metabolic disorders in mice, which in turn triggers a series of lipid metabolic disorders, such as obesity[17]. Therefore, sufficient estrogen is a critical factor for maintaining normal TC metabolism. This specifically reflects the interdependence and interpromotion between estrogen and TC.

Estrogen and pregnenolone

Pregnenolone is synthesized from cholesterol in the mitochondria of cells via the actions of steroidogenic acute regulatory protein (StAR) (StAR) and cytochrome P450 family 11 subfamily A member 1 (CYP11A1) enzyme[12,18]. This process represents the first step in the steroid hormone biosynthesis pathway, and thus pregnenolone is often referred to as the "parent steroid"[19,20]. First, pregnenolone can be converted to progesterone via 3β-hydroxysteroid dehydrogenase (HSD3B)[18]. Second, pregnenolone can be converted to 17α-hydroxypregnenolone, and the latter is then converted to dehydroepiandrosterone (DHEA) via the action of CYP17A1 enzyme, where DHEA is a precursor of androgens[21]. Third, in the adrenal glands, pregnenolone can also be converted to adrenal cortical hormones such as cortisol and aldosterone[12]. It has been found that estrogen can increase the synthesis of pregnenolone precursor in the mitochondria of rabbit corpus luteum[22]. This suggests that estrogen may regulate steroidogenesis by influencing the conversion of cholesterol to pregnenolone.

Estrogen and progestogen

Estrogen and progesterone, mainly produced by the ovaries during the menstrual cycle, jointly regulate the function of the female reproductive tract and are key components of endocrine balance[23]. In the steroid biosynthesis pathway, pregnenolone can be converted to progesterone, which, as a critical intermediate, is transformed into 17α-hydroxyprogesterone via 17α-

hydroxylase, participating in the synthesis of androgens and estrogen[12] (Fig. 2).

Both act through ligand-binding receptors (as transcription factors) and membrane receptor-mediated signaling cascades, interacting in multiple physiological processes[23]: during the menstrual cycle, estrogen promotes follicle growth and endometrial thickening, while progesterone prepares for implantation, fluctuations in their levels regulate menstruation[24]; during pregnancy, they jointly maintain endometrial stability and promote fetal development[25]; they also affect synaptic plasticity for neuroprotection[26], breast development (linked to breast cancer)[27], and cardiovascular health (e.g., regulating blood lipids)[13]. Additionally, there is bidirectional influence, as exemplified by the finding that estradiol inhibits basal progesterone production in cultured porcine granulosa cells in a time- and dose-dependent manner[28].

Estrogen and androgen

Androgens (e.g., testosterone and androstenedione) serve as precursors of estrogen, with specific conversion pathways: androstenedione is converted to estrone by ARO1, and estrone is further transformed into 17β-estradiol via 17β-hydroxysteroid dehydrogenase[8]; testosterone can also be directly converted to estradiol by ARO1[9]. This process occurs in various tissues, including the testes[29], ovaries, adrenal glands, and peripheral tissues such as bone[30] and adipose tissue (Fig. 3).

The two hormones interact in multiple physiological functions: in the reproductive system, estrogen is crucial for sex determination in non-mammalian vertebrates, and co-administration of androgen and estrogen may lead to feminization of gonadal phenotypes[9]. ARO1 in the male testes can convert androgen to estrogen, which is essential for sperm maturation and storage[29,31]. In the *ARO1* knockout mice constructed in the author's laboratory, sterility was observed in homozygous male mice, indicating that ARO1 is a necessary condition for sperm maturation. Meanwhile, inhibition of ARO1 activity by letrozole disrupts the synthesis pathway of androgen conversion to estrogen, leading to a decrease in endogenous estrogen levels[32]. This precisely reflects the scientific connotation of the interdependence of Yin and Yang. Although *ARO1* knockout homozygous female mice exhibit ovarian and uterine atrophy as well as infertility, endogenous estradiol remains at a relatively high level. It suggests that there is a second estrogen synthesis

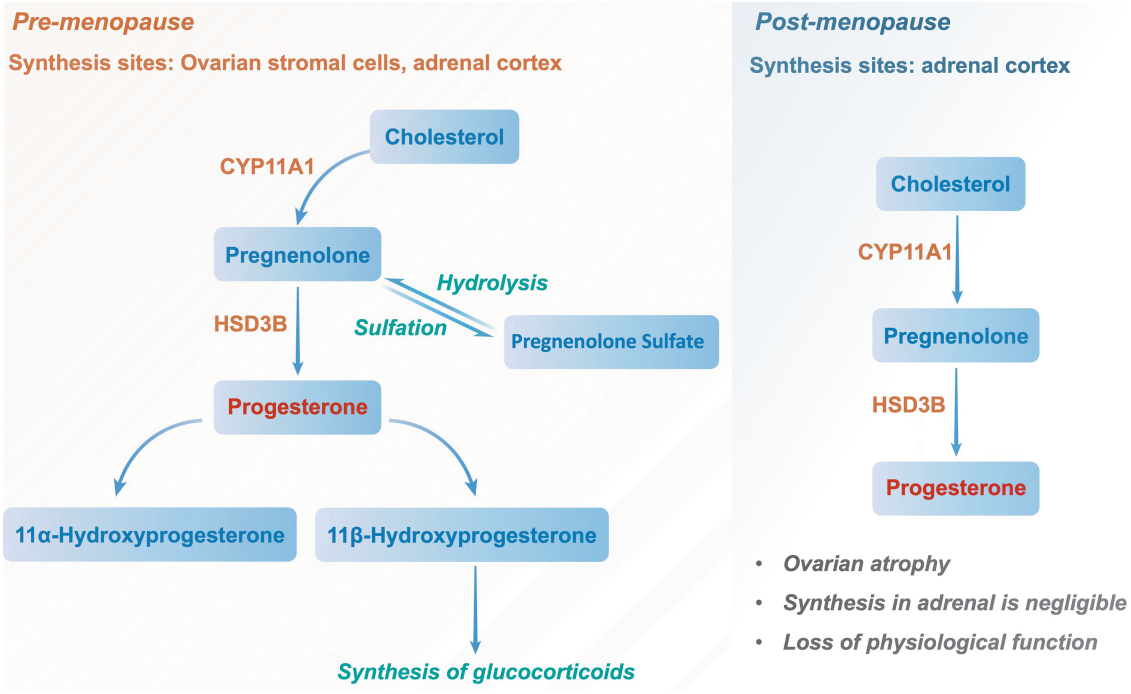

Figure 2: Progestogen synthesis pathway.

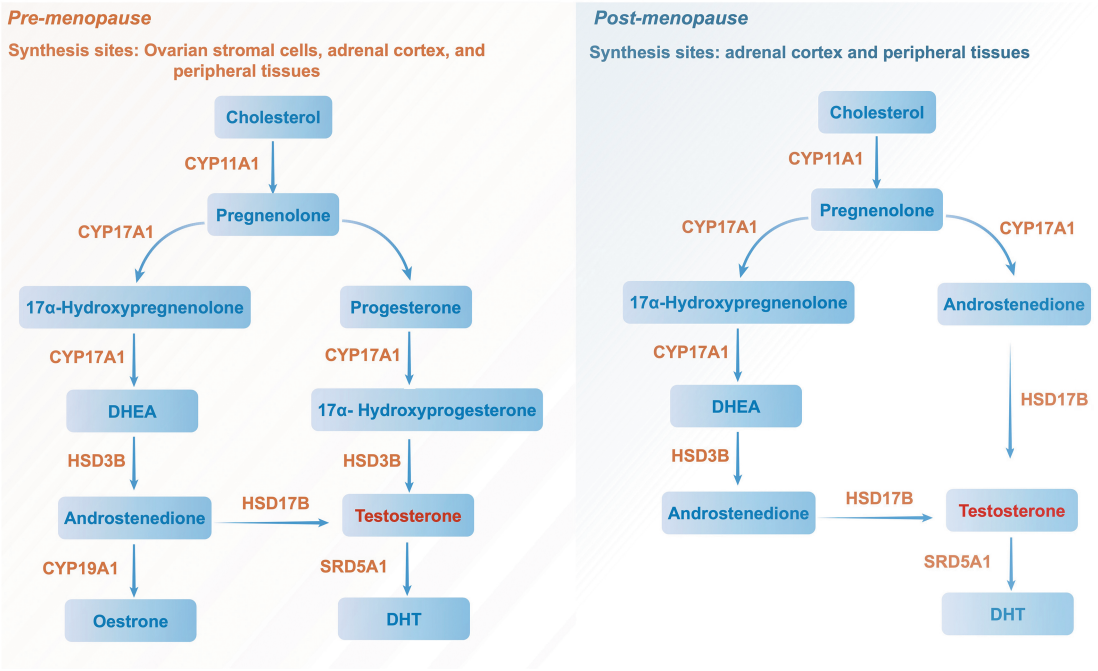

Figure 3: Androgen synthesis pathway. DHEA: dehydroepiandrosterone. DHT: dihydrotestosterone.

pathway besides ARO1, which requires further exploration. Moreover, their receptors, along with progesterone receptors and growth hormone receptors, are expressed in vascular malformations[33]. For bone health, bone, as an endocrine tissue expressing both hormone receptors and steroid-metabolizing enzymes, is jointly influenced by estrogen and androgen in terms of sexual dimorphism[30]. In immune function, their receptor signaling pathways directly regulate immune responses at the transcriptional level, affecting outcomes of cancer, autoimmune diseases, and infectious diseases—for instance, estrogen modulates anti-inflammatory responses and antibody production in macrophages and B cells, while androgen influences the activity of natural killer (NK) cells and T cells[34]. In the nervous system, estrogen can regulate serotonin synthesis and metabolism, affecting pain perception (potentially linked to the higher incidence of migraines in women). In skin health, estrogen exerts protective effects, whereas androgen acts oppositely[35].

Summary and outlook

This study explores the scientific connotation of Yin-Yang interdependence and interpromotion in TCM using the estrogen synthesis pathway as a biological model. It clarifies that Yin-Yang interdependence means mutual reliance between cholesterol (Yin, raw material) and key enzyme activity (Yang, function) in estrogen synthesis, where neither works alone. Mutual promotion refers to synergistic enhancement, as seen when androgens (Yin) are aromatized to estrogens by ARO1/CYP19A1 (Yang). The study also details estrogen synthesis (from cholesterol via progestogen, androgen) and its interactions with cholesterol, progestogen, and androgen. Notably, *ARO1*-knockout homozygous male mice are sterile (ARO1 vital for sperm maturation), while females still reproduce, hinting at an alternative estrogen pathway.

Future research should first identify the alternative estrogen synthesis pathway in *ARO1*-knockout female mice to fill knowledge gaps. Second, deeper exploration of Yin-Yang relationships in estrogen-related physiological/pathological processes (e.g., cardiovascular protection, bone health) could offer new TCM-informed therapeutic targets. Finally, combining TCM Yin-Yang theory with modern technology may uncover more biological mechanisms, advancing both traditional medicine and steroid hormone research.

Author contributions

Wei Zhang: Writing and revision of the article. Xiang Li:

Revision of the article. Linhua Zhao: Final approval of the published version.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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