Journal of Steroid Biochemistry & Molecular Biology 145 (2015) 133–138

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry & Molecular Biology

journal homepage: www.elsevier.com/locate/jsbmb

Review

All sex steroids are made intracellularly in peripheral tissues by the mechanisms of intracrinology after menopause

Fernand Labrie *

EndoCeutics Inc., Quebec City, Canada

ARTICLE INFO

Article history:
Received 11 April 2014
Received in revised form 21 May 2014
Accepted 6 June 2014
Available online 9 June 2014

Keywords:
Intracrinology
Menopause
Estrogens
Androgens
Dehydroepiandrosterone
Breast cancer

ABSTRACT

Following the arrest of estradiol secretion by the ovaries at menopause, all estrogens and all androgens in postmenopausal women are made locally in peripheral target tissues according to the physiological mechanisms of intracrinology. The locally made sex steroids exert their action and are inactivated intracellularly without biologically significant release of the active sex steroids in the circulation. The level of expression of the steroid-forming and steroid-inactivating enzymes is specific to each cell type in each tissue, thus permitting to each cell/tissue to synthesize a small amount of androgens and/or estrogens in order to meet the local physiological needs without affecting the other tissues of the organism.

Achieved after 500 million years of evolution, combination of the arrest of ovarian estrogen secretion, the availability of high circulating levels of DHEA and the expression of the peripheral sex steroid-forming enzymes have permitted the appearance of menopause with a continuing access to intratissular sex steroids for the individual cells/tissues without systemic exposure to circulating estradiol. In fact, one essential condition of menopause is to maintain serum estradiol at biologically inactive (substhreshold) concentrations, thus avoiding stimulation of the endometrium and risk of endometrial cancer. Measurement of the low levels of serum estrogens and androgens in postmenopausal women absolutely requires the use of MS/MS-based technology in order to obtain reliable accurate, specific and precise assays. While the activity of the series of steroidogenic enzymes can vary, the serum levels of DHEA show large individual variations going from barely detectable to practically normal "premenopausal" values, thus explaining the absence of menopausal symptoms in about 25% of women. It should be added that the intracrine system has no feedback elements to adjust the serum levels of DHEA, thus meaning that women with low DHEA activity will not be improved without external supplementation. Exogenous DHEA, however, follows the same intracrine rules as described for endogenous DHEA, thus maintaining serum estrogen levels at substhreshold or biologically inactive concentrations. Such blood concentrations are not different from those observed in normal postmenopausal women having high serum DHEA concentrations. Androgens, on the other hand, are practically all made intracellularly from DHEA by the mechanisms of intracrinology and are always maintained at very low levels in the blood in both pre- and postmenopausal women.

Proof of the importance of intracrinology is also provided, among others, by the well-recognized benefits of aromatase inhibitors and antiestrogens used successfully for the treatment of breast cancer in postmenopausal women where all estrogens are made locally. Each medical indication for the use of DHEA, however, requires clinical trials performed according to the FDA guidelines and the best rules of clinical medicine.

Contents

* Corresponding author at: EndoCeutics Inc., 2795 Laurier Blvd, Suite 500, Quebec G1 V 4M7, Canada. Tel.: +1 418 653 0055.
E-mail address: fernand.labrie@endoceutics.com (F. Labrie).

http://dx.doi.org/10.1016/j.jsbmb.2014.06.001
0960-0760/

1. Introduction

The negative impact of hormone deficiency after menopause is well known. These problems pertain to hot flushes, night sweats, vulvovaginal atrophy (vaginal dryness, pain at sexual activity, irritation/itching), bone loss and fractures, sexual dysfunction, muscle loss, loss of memory, loss of cognition and possibly Alzheimer's disease [1–7]. With the longer life span and the increased world population, more than 1.1 billion postmenopausal women are expected by 2025 with the majority of them expected to suffer from menopausal signs and symptoms [8]. The problems mentioned above also have an economic impact, the costs of menopausal symptoms being illustrated by the 10–15% lower work productivity, 23% more sick days and 40% higher health-related costs [9].

1.1. What is the exact cause of hormone deficiency after menopause?

Menopause corresponds to the cessation of reproductive life secondary to the depletion of primordial follicles accompanied by an arrest of estrogen and progesterone secretion by the ovaries. Based on the knowledge that ovarian estrogen secretion ceases at menopause in all women, systemic and local estrogens have so far been the traditional and practically exclusive treatment of vulvovaginal atrophy and hot flushes, these two most frequent symptoms of menopause affecting approximately 75% of post-menopausal women.

Since ovarian estrogen secretion stops in all women at menopause, and not all women suffer from the menopausal symptoms and signs mentioned above, there must be another factor or another variable source of sex steroids which could explain why some women are clinically free from menopausal symptoms while others (about 75%) suffer from menopausal symptoms and signs at various degrees [10–12].

2. Data review and discussion

2.1. After cessation of estrogen secretion by the ovaries at menopause, sex steroids continue to be required and are provided exclusively by intracrine local formation

Without the action of the estrogens and androgens made specifically by the mechanisms of intracrinology in each cell type of each tissue from circulating DHEA of adrenal (~80%) and ovarian (~20%) origins [13] (Fig. 1), the problems presently affecting women at menopause, especially osteoporosis and fractures, hot flushes, muscle loss, type II diabetes, vulvovaginal atrophy, sexual dysfunction, memory loss, cognition loss and possibly Alzheimer's disease, would be much more serious than presently observed with a likely greater reduction in lifespan. In other words, while serum estradiol must remain at subthreshold or inactive concentrations in the blood stream after menopause (Fig. 2), the normal functioning of peripheral tissues (except the endometrium)

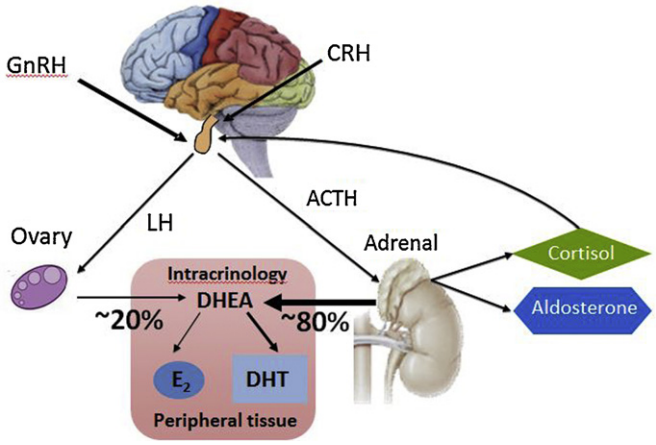

Fig. 1. Schematic representation of dehydroepiandrosterone (DHEA) as the unique source of sex steroids after menopause. Approximately 80% of circulating DHEA is of adrenal origin while about 20% is released from the ovary [13]. Accordingly, after menopause, all estrogens and all androgens are made locally from DHEA in peripheral target tissues by the mechanisms of intracrinology. The amount of sex steroids made depends upon the level of the steroid-forming enzymes specifically expressed in each cell in each tissue (Fig. 3). GnRH, gonadotropin releasing hormone; LH, luteinizing hormone; CRH corticotropin releasing hormone; ACTH, adrenocorticotropic hormone.

requires intracellular physiological concentrations of estrogens and/or androgens (Figs. 3 and 4).

Medical research, however, has concentrated almost exclusively on the arrest of estradiol and progesterone secretion by the ovaries and how to replace ovarian estrogens. One never envisaged that

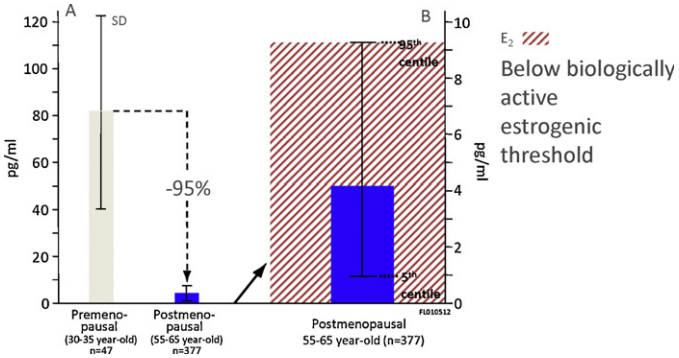

Fig. 2. Maintenance of serum estradiol at biologically inactive levels in postmenopausal women. (a) Illustration of the ≥95% fall in circulating estradiol between 30–35 year-old premenopausal women ($n = 47$) and 55–65-year-old postmenopausal women ($n = 377$) [13]. Data are presented as means ± SD. (b) Illustration of the range of biologically non significant or subthreshold serum estradiol concentrations in normal postmenopausal women. Such low levels of circulating estradiol are below the threshold of estrogenic activity (hatched area) and have no biological relevance, thus avoiding stimulation of cell proliferation in the uterus and other inappropriate tissues.