

Following the publication of the Opinion entitled "Wishing a dream came true: DHEA as a rejuvenating treatment" by O.T. Wolf and C. Kirschbaum (*J. Endocrinol. Invest.* 21: 133, 1998), the following paper by F. Labrie is another opinion on the same hot topic. We thank both the Authors for their kind contributions and leave to the reader the possibility to evaluate these two different points of view about the potential clinical usefulness of DHEA.

The Editor-in-Chief

OPINION

## DHEA as physiological replacement therapy at menopause

F. Labrie

Laboratory of Molecular Endocrinology, Laval University Medical Research Center, Québec, G1V 4G2, Canada

The human is unique with other primates among all other species in having adrenals which secrete large amounts of the steroid precursors dehydroepiandrosterone (DHEA) and its sulfate derivative DHEA-S. The concentration of DHEA-S in the human circulation is the highest among all steroids and is surpassed only by cholesterol, the blood levels of DHEA-S being 5-fold higher than those of cortisol in young men and women. During aging, however, there is a dramatic decrease in the circulating levels of both DHEA and DHEA-S, the decrease between the ages of 20-30 years and 50-60 years being already of the order of 60% (1-4).

During the course of studies performed in prostate cancer patients who had surgical castration or were medically castrated with an LHRH agonist, it was found, somewhat surprisingly, that the intraprostatic concentration of dihydrotestosterone (DHT), the most potent androgen, is only reduced by 50 to 60% after castration, thus leaving high levels of androgens in the prostate (5, 6).

We now know that these intraprostatic androgens originate from the local transformation of DHEA-S and DHEA into DHT in the prostatic tissue itself. The biosynthesis of DHT occurs in both normal and malignant tissue. This new field of endocrinology has been called intracrinology in order to focus our attention on the mechanisms by which DHEA, an in-

active precursor, is transformed locally in peripheral target tissues into active androgens or estrogens, depending upon the enzymes specifically expressed in each cell type of each tissue (7-9) (Fig. 1). Thus, each peripheral cell type possesses a specific set of steroidogenic enzymes which synthesize androgens and/or estrogens according to the local needs. This mechanism of intracrinology has at least three advantages, the first one being that only the tissues which express the specific enzymes make and are thus exposed to the androgens and/or estrogens required for their physiological activity. Consequently, the other tissues are spared of the unwanted exposure to sex steroids. A third benefit is that the formation of sex steroids in the same cells where their action is exerted implies that a minimal amount of hormone is required for maximal action, thus avoiding the marked loss caused by metabolism when steroids are transported in the blood and pass through the liver before reaching their site of action. At the present time, most of the enzymes required to transform DHEA and DHEA-S into androgens and/or estrogens in human tissues have been isolated, their structure elucidated and important knowledge has already been obtained about the characteristics of their actions (9-11).

The genetic, biochemical, and physiological knowledge gained during the last 10 years about the steroidogenic enzymes expressed in peripheral tissues provides an explanation for at least a high proportion of the effects of DHEA. In fact, all the effects of DHEA that we have described can be explained by the action of the androgens and/or estrogens synthesized from DHEA in each target cell in each peripheral tissue.

While a long series of experimental data, mainly

©1998, Editrice Kurtis

**Key-words:** DHEA, menopause, HRT, hormone replacement therapy, osteoporosis, vaginal atrophy.

**Correspondence:** Professor Fernand Labrie, Laboratory of Molecular Endocrinology, CHUL Research Center, 2705 Laurier Boulevard Québec, Québec, G1V 4G2, Canada.

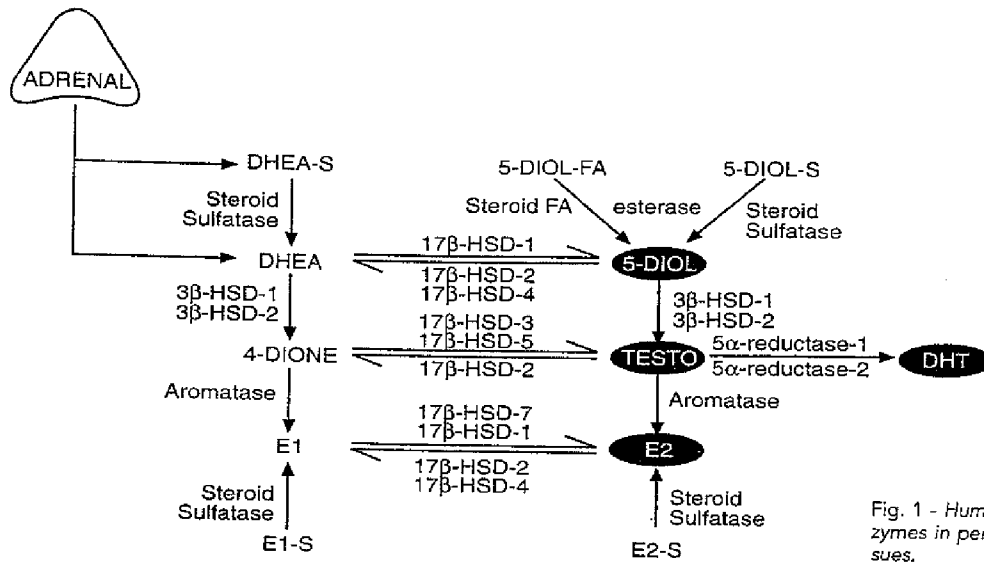


Fig. 1 - Human steroidogenic enzymes in peripheral intracrine tissues.

obtained in laboratory animals and *in vitro* models, suggest an important role of DHEA in a long series of diseases, much information remains to be gained before rigorous scientific evidence is obtained on the definitive role of DHEA in the human. In this context, our recent studies where DHEA was administered for 12 months to 60-70 year-old postmenopausal women have identified important benefits of DHEA in these subjects. The most important benefit is probably the stimulation of bone mineral density (10), an effect most likely due to be the local transformation of DHEA into androgens. This mechanism is well supported by detailed experimental data performed in the rat where we have found that the marked stimulation of bone mineral density is almost completely blocked by concomitant administration of a pure antiandrogen, namely Flutamide. This finding of a stimulation of bone formation by DHEA is particularly important since the currently available drugs for the treatment and prevention of osteoporosis in women do not stimulate bone formation but only reduce the rate of bone loss. These pertain to estrogens, bisphosphonates, calcitonin, and the recently developed selective estrogen receptor modulators (SERMs), such as Raloxifene.

Another benefit observed in our study (10) is a stimulatory effect of DHEA on the vaginal mucosa, this effect being similar to that achieved by estrogens. The advantage of DHEA over estrogens, however, is that DHEA has no stimulatory effect on the endometrial mucosa which remains completely at-

rophic, thus eliminating the need to use a progestin. It should also be mentioned that DHEA has been found to have a marked inhibitory effect on the development and growth of dimethylbenz(a)anthracene (DMBA)-induced mammary tumors in the rat (12, 13). Most importantly, we have recently observed that DHEA inhibits the growth of the human ZR-75-1 human breast cancer xenografts in nude mice (14).

During our 12-month study of DHEA replacement therapy in postmenopausal women, we have also observed that treatment with DHEA decreases basal serum levels of glucose and insulin, thus suggesting a beneficial effect of such treatment on insulin resistance, a common problem observed during aging. A decrease of subcutaneous fat and an increase in muscular mass measured at the level of the thigh was also observed in our study. Well-being was also improved in 80% of subjects, a finding similar to that reported by Morales et al. (15). The above-summarized study indicates that DHEA stimulates bone formation, thus increasing bone mineral density while it exerts a stimulatory estrogenic effect on the vagina and it inhibits the development and growth of breast cancer. Not only DHEA replacement therapy could avoid the risk of breast cancer associated with estrogens (also possibly with progestins), but the lack of effect of DHEA on the endometrium eliminates the risk of endometrial cancer.

A potential application of DHEA is its use as hormone replacement therapy in women at menopause

in order to compensate for the marked decrease in the secretion of this steroid well known to occur during aging. The potential advantages of DHEA have been mentioned above, namely stimulation of bone mineral density and vaginal maturation, while avoiding the potential negative effects of estrogen-replacement therapy on the breast and uterus.

Further clinical studies, however, are needed in order to assess with more precision these and other beneficial effects of DHEA in post-menopausal women. There is no doubt, however, that this steroid is efficiently transformed into androgens and/or estrogens in specific target intracrine tissues, depending upon the nature and level of expression of each of the steroidogenic enzymes in each cell type (1) (Fig. 1). Some tissues, such as the bone and sebaceous glands, mainly transform DHEA into androgens while the vaginal mucosa transforms DHEA into estrogens. The endometrial epithelium, on the other hand, does not possess these enzymes and no effect of DHEA is thus seen. The inhibitory effect of DHEA on breast cancer development and growth observed in the DMBA model and the inhibition of breast cancer proliferation observed in xenografts of human ZR-75-1 tumors, clearly indicate the potential beneficial effects of DHEA on breast cancer.

## REFERENCES

1. Labrie F., Bélanger A., Cusan L., Candas B. Physiological changes in DHEA are not reflected by the serum levels of active androgens and estrogens but of their metabolites: intracrinology. *J. Clin. Endocrinol. Metab.* 82: 2403, 1997.
2. Bélanger A., Candas B., Dupont A., Cusan L., Diamond P., Gomez J.L., Labrie F. Changes in serum concentrations of conjugated and unconjugated steroids in 40- to 80-year-old men. *J. Clin. Endocrinol. Metab.* 79: 1086, 1994.
3. Orentreich N., Brind J.L., Rizer R.L., Vogelman J.H. Age changes and sex differences in serum dehydroepiandrosterone sulfate concentrations throughout adulthood. *J. Clin. Endocrinol. Metab.* 59: 551, 1984.
4. Labrie F., Bélanger A., Cusan L., Gomez J.L., Candas B. Marked decline in serum concentrations of adrenal C19 sex steroid precursors and conjugated androgen metabolites during aging. *J. Clin. Endocrinol. Metab.* 82: 2396, 1997.
5. Labrie F., Dupont A., Belanger A. Complete androgen blockade for the treatment of prostate cancer. In: de Vita V.T., Hellman S., Rosenberg S.A. (Eds.), *Important Advances in Oncology*. J.B. Lippincott, Philadelphia, 1985, p. 193.
6. Bélanger A., Brochu M., Cliche J. Levels of plasma steroid glucuronides in intact and castrated men with prostatic cancer. *J. Clin. Endocrinol. Metab.* 62: 812, 1986.
7. Labrie F. Intracrinology. *Mol. Cell. Endocrinol.* 78: C113, 1991.
8. Labrie F., Simard J., Luu-The V., Bélanger A., Pelletier G., Morel Y., Mebarki F., Sanchez R., Durocher F., Turgeon C., Labrie Y., Rheume E., Labrie C., Lachance Y. The 3-hydroxysteroid dehydrogenase/isomerase gene family: lessons from type II 3 $\beta$ -HSD congenital deficiency. In: Hansson V., Levy F.O., Tasken K. (Eds.), *Signal Transduction in Testicular Cells*. Ernst Schering Research Foundation Workshopringer-Verlag, Berlin, Heidelberg, New York, 1996, p. 185.
9. Labrie F., Luu-The V., Lin S.X., Labrie C., Simard J., Breton R., Blanger A. The key role of 17 $\beta$ -HSDs in sex steroid biology. *Steroids* 62: 148, 1997.
10. Labrie F., Diamond P., Cusan L., Gomez J.L., Belanger A. Effect of 12-month DHEA replacement therapy on bone, vagina, and endometrium in post-menopausal women. *J. Clin. Endocrinol. Metab.* 82: 3498, 1997.
11. Biswas M.G., Russell D.W. Expression cloning and characterization of oxidative 17 $\beta$ - and 3 $\alpha$ -hydroxysteroid dehydrogenase from rat and human prostate. *J. Biol. Chem.* 272: 15959, 1997.
12. Li S., Yan X., Belanger A., Labrie F. Prevention by dehydroepiandrosterone of the development of mammary carcinoma induced by 7,12-dimethylbenz(a)anthracene (DMBA) in the rat. *Cancer Res. Treat.* 29: 203, 1993.
13. Luo S., Labrie C., Labrie F. Prevention of development of dimethylbenz(a)anthracene (DMBA)-induced mammary carcinoma in the rat by the new nonsteroidal antiestrogen EM-800. *Breast Cancer Res. Treat.* in press, 1998.
14. Couillard S., Labrie C., Belanger A., Candas B., Labrie F. Inhibitory effect of dehydroepiandrosterone and of the novel antiestrogen EM-800 on the growth of human ZR-75-1 breast cancer xenografts in nude mice. *J. Natl. Cancer Inst.* in press, 1998.
15. Morales A.J., Nolan J.J., Nelson J.C., Yen S.S. Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age. *J. Clin. Endocrinol. Metab.* 78: 1360, 1994.