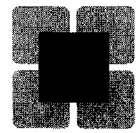

Androgenesis and androdynamics in normal women

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■ The effects of estrogenic steroid hormones in women are apparent, but the circulating androgen levels are much higher. Compared with serum estrone and estradiol levels, circulating testosterone levels are five to 10 times higher, androstenedione levels 30 times higher, dehydroepiandrosterone levels 100 times higher, and dehydroepiandrosterone sulfate levels 40,000 times higher. Androgen production in women is physiologically appropriate, but it differs from other hormonal systems in that there seem to be no mechanisms controlling the serum levels. Androgens are produced almost incidentally from reproductive and ACTH-adrenal axes. No distinct feedback systems have been identified for the androgens, although the lifetime patterns of changes, particularly of adrenal androgens, suggest that such systems should exist. Normal androgenesis from the two axes and the mechanisms of androgen action are described, as an introduction to abnormal androgen action in women.

□INDEX TERM: ANDROGENS □ CLEVE CLIN J MED 1990; 57:161–166

THE OVARIES AND ADRENALS both manufacture androgens from free cholesterol. Most cholesterol is derived from intracellular stores of cholesterol or circulating low-density lipoprotein cholesterol interiorized through receptor pits on the membrane.[1] The steroid hormones are synthesized in both the ovary and the adrenals by modifying the basic cholesterol molecule in a series of enzymatic steps.[2,3] Two parallel pathways permit synthesis of the androgens dehydroepiandrosterone (DHEA) and androstenedione. Testosterone, the estrogens, and dehydroepiandrosterone sulfate (DHEAS) are then derived by further metabolism from these precursor compounds. The major adrenal products are cortisol and aldosterone; the most important ovarian products are estrogens and progesterone. The adrenal gland produces no significant quantities of estrogen or progesterone, and the ovary produces no cortisol or aldosterone. While the basic synthetic pathways of androgens are similar, there are considerable differences in the process and control of steroidogenesis in the sites.

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ANDROGEN PRODUCTION IN THE HYPOTHALAMIC-PITUITARY-OVARIAN AXIS

Reproductive function in women is coordinated through the hormonal changes of the menstrual cycle, a biological rhythm that integrates the development and release of a mature ovum with structural and functional changes in the uterus, cervix, and fallopian tubes. In the absence of pregnancy, the menstrual flow occurs on an approximately monthly basis as the external expression of the repetitive functioning of the hypothalamic-pituitary-ovarian axis. The regulation of ovarian function is

mediated through the release of gonadotropin-releasing hormone (GnRH) that controls the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland. LH and FSH are, in turn, directly responsible for selection and maturation of the dominant follicle, ovulation, and luteinization of the follicle. Accompanying the anatomical changes is a series of well-coordinated fluctuations in circulating levels of ovarian steroid hormones, particularly estradiol and progesterone. These hormones are responsible for the development of the endometrium, and their withdrawal toward the end of the cycle leads to the shedding of the lining of the uterus.

Androgen production in the ovary is a continuing function of ovarian stromal cells and occurs in the temporary endocrine gland in the developing follicle as a function of thecal cells. In both sites, androgen production is the result of the LH action via receptors in the membrane, which are continually present on stromal cells and are found on the developing thecal cells.[4] FSH receptors are found on mature granulosa cells but are not developed in immature cells.[5] Granulosa cells lack a 17-20 lyase and thus cannot manufacture androgens.[2-3,6] FSH induces in the granulosa cells the aromatase enzyme that converts androgens to estrogens.[7-10] The androgens produced in the thecal cells serve as precursors for the production of estradiol in the granulosa cells. Estradiol is manufactured as part of a two-step, two-gonadotropin, two-cell procedure. Androgenic precursors are manufactured in the thecal cell, stimulated by LH. The androgens, predominantly androstenedione, cross the basement membrane into the granulosa cells to be transformed by the aromatase enzyme into estrogens, predominantly estradiol for local use and for the systemic circulation. It seems that androgens are released or escape into circulation but play little significant role in the feedback control of GnRH-gonadotropin release in normal circumstances.

The control of androgen production in the ovary is mostly the result of LH action. Other hormones have a permissive role, but there is little good evidence of a direct role for any hormone other than prolactin,[11] which may also be involved in the regulation of adrenal androgenesis. However, there are no clear regulatory mechanisms other than LH.

ANDROGEN PRODUCTION IN THE ACTH-ADRENAL AXIS

The location of androgen production in the adrenal gland is generally described as the reticularis, but substantial quantities of DHEAS, DHEA, testosterone, and androstenedione are found in both the zona fasciculata and the reticularis.[12,13] In the reproductive-age adult, the adrenal cortex produces androstenedione and DHEA in episodic bursts that are synchronous with ACTH-cortisol release.[14-16] Administration of ACTH elevates both hormones together with cortisol.[17] The sulfate ester of DHEA has a half-life exceeding 24 hours and a clearance rate that is not affected by age.[18,19]

In contrast to the other androgens, DHEAS has no significant circadian variations.[14,16] However, DHEAS does increase in response to ACTH, albeit more slowly than the other adrenal androgenic hormones.[20] Therefore, although it is without significant androgenic activity, DHEAS has proven useful as a marker for adrenal androgen production.

The increase in the basal values of these hormones and their capacity to respond to ACTH occur prior to and during early puberty, reach a maximum during adult life, and fall again with advancing age.[21-24] In contrast, neither ACTH nor cortisol has any significant fluctuations matching the lifetime chronological patterns of the adrenal androgenic hormones.[25,26] The ability to respond to ACTH and the loss of that ability correspond with the acquisition and loss of microsomal 17-hydroxylase and 17-20 desmolase in the adrenal cortex.[27]

The coordination of adrenarche as part of puberty suggests that at least one non-local factor is important in adrenal androgen regulation. A pituitary "cortical androgen-stimulating hormone" was proposed because ACTH administered to individuals with hypopituitarism was capable of stimulating a normal cortisol response, but the adrenal androgen response was considerably reduced.[28] In a comparable animal model, bovine pituitary extract produces a relatively greater androgen-stimulating effect in castrated hypophysectomized dogs than ACTH alone.[29,30] The nature of the factor remains obscure, although in vitro evidence has further defined its characteristics.

Other pituitary hormones have been considered. Elevated prolactin levels have been linked to increased androgen levels during reproductive life, and both hirsutism and a syndrome similar to polycystic ovarian disease have been described with hyperprolactinemia.[31,32] Growth hormone may, in part, regulate intrauterine adrenal androgen production.[33] However, other evidence linking either growth hormone or prolactin to adrenal androgenesis during adult life is scant, and neither hormone has long-term changes matching the chronological pattern of adrenal androgens throughout life. Other pituitary products, such as endogenous opiates and alpha-melanocyte-stimulating hormone, have

also been linked with regulation of androgen production by the adrenal, but the evidence supporting these hormones as modulators of adrenal androgenesis is scant.

The most clear chronological relationship is between adrenal androgens and reproductive status; therefore, pituitary-ovarian relationships have been evaluated with particular interest. The enzymes induced at puberty decline following menopause.[27] Gonadotropins have no direct effect on adrenal androgen synthesis, nor is there any relationship between adrenal androgens and gonadotropins in the agonadal individual.[34] Early in vitro and in vivo evidence suggested that estrogen may increase adrenal androgen levels.[35–37] The levels of DHEAS and other androgens fall in old age to approximately 20% of reproductive age values. Therefore, to establish separate relationships, gonadal function must be considered as a factor independent of age. This was investigated in women with impaired gonadal function throughout and beyond the normal reproductive age range. It was clear that DHEAS levels were significantly lower in women with premature ovarian failure and castration during the reproductive age range and even in women with hypothalamic amenorrhea when compared to control women with normal reproductive function.[24] The levels did, however, decrease further with increasing age so that levels in postmenopausal women were lower than in reproductive age women with ovarian failure. The levels in castrated women in the postmenopausal age range were the lowest of all the groups, suggesting that even at this age the gonad is important in the regulation of sex-steroid manufacture in the adrenal. Lobo et al[38] provided evidence that estradiol pellet insertion at the time of castration prevented a decrease in the adrenal androgens. Others investigating at various times throughout the reproductive age range have denied such an effect.[39–42] All of these studies were, however, of relatively short duration. Cumming et al[24] demonstrated that 10 years of estrogen therapy makes no difference to circulating DHEAS levels compared with a control group of similar age that had received no estrogen therapy in the previous 10 years.

One final problem in accepting estrogen as an adrenal androgen-stimulating hormone comes from the early investigations in vitro, in which it was demonstrated that estrogen had an inhibitory effect on the delta 4-5 isomerase/3β-ol dehydrogenase enzyme.[35,43] This would be likely to elevate DHEA but not androstenedione. The period of enhanced adrenal responsiveness is associated with the presence of microsomal 17 hydroxylase and 17-20 desmolase promoting the production of all androgens on both the pathways.[27] This raises the intriguing possibility that the ovary may produce a nonsteroidal substance that influences sex-steroid synthesis in the adrenal.[24] However, this remains unproven. Other factors such as body composition[44] and physical exercise[45] may also influence DHEAS levels independent of gonadal function; all of these areas remain to be explored further.

CONTRIBUTIONS FROM THE OVARY AND ADRENAL

Assessments of the relative contributions of the ovary and the adrenal are based on a number of methods, none of them particularly accurate. The methods include examination of serum levels of patients without adrenal glands[46] or ovaries,[24] direct cannulation, evaluation of lifetime patterns of change as previously described, and stimulation and suppression tests of the specific organ concerned.[24,46–48] The most commonly accepted figures suggest that testosterone, androstenedione, and dihydrotestosterone are derived about half each from the ovary and the adrenal.[47] Conversely, DHEA and DHEAS are respectively 80% and 95+% derived from adrenal.[47] Therefore, DHEAS has tended to replace 17KS as a measure of adrenal function, particularly as levels are stable with little diurnal variation or monthly cyclic variations.[49,50]

However, the situation is further complicated since circulating androgens can be derived from direct secretion and/or peripheral metabolism of other sex steroids.[47,51] Thus it is generally accepted that almost all of the dihydrotestosterone and about half of the circulating testosterone is derived from conversion of precursors already in circulation. Dihydrotestosterone is derived from androstenedione and testosterone while conversion of androstenedione is responsible for almost all of the testosterone arising from peripheral sources. Almost all androstenedione, DHEA, and DHEAS come from direct secretion. There is no understanding of what controls the peripheral conversion of steroids, nor is it clear whether the conversion can occur in the liver, lungs, skin, or fat.

If samples are taken daily through the cycle, basal- and dexamethasone-suppressed testosterone and androstenedione vary with cyclic changes of estrogen.[47] It seems odd that 10 to 100 times more androgen may "leak out" just to permit estrogens to be manufactured. However, there does not appear to be any significant feedback of androgens on LH levels in the normally menstruating woman. Administration of human chorionic gonadotropin acting as an LH substitute increases testosterone levels.[52] Surprisingly, perhaps, dihy-

drotestosterone shows little diurnal variation through the cycle, either basal or when suppressed with dexamethasone.[48] In contrast, DHEA and DHEAS show little menstrual variation.[48]

ANDROGENS IN CIRCULATION

Androgens in circulation are influenced by protein binding. The 17β sex steroids (testosterone, dihydrotestosterone, and estradiol) are bound selectively to sex-hormone-binding globulin (SHBG). Testosterone also binds in a nonspecific manner to capillary blood glucose and albumin while a small amount is biologically free. SHBG preferentially binds testosterone so that alterations in the level of SHBG produce a differential effect on the biologically available free levels of estradiol.[53] Increasing levels of SHBG produce relatively lower quantities of free testosterone ν estradiol while decreasing SHBG levels produce relatively larger quantities of free testosterone ν estradiol. The system, therefore, may act as an amplifier of biological activity. The levels of SHBG change with a number of influences. Increased values occur with estrogens and thyroxine while androgens (including androgenic gestagens) and excess quantities of cortisol and growth hormone decrease SHBG production.

It remains to be determined what proportion of the circulating testosterone is biologically available; that is, which proportion can cross the membranes into the target cell. The half-disassociation time of albumin-testosterone is sufficient to permit substantial cross-membrane transfer of albumin-bound testosterone within its time of capillary transit.[54] Increasing evidence supports the conclusion that non-SHBG-bound testosterone rather than free (that is, unbound to either albumin or SHBG) may be better correlated with androgen activity.[55,56]

MODE OF ACTION AND CLEARANCE OF ANDROGENS

When testosterone crosses into the cell, it is converted into dihydrotestosterone by 5α reductase, binds to a receptor, and by interaction with the nucleus of the cell produces messenger RNA, which is then used to manufacture protein appropriate for the needs of the cell.[57] A degradation product of dihydrotestosterone, 3α androstanediol, and its glucuronide form have been suggested as measures of peripheral testosterone utilization.[58]

Studies of hepatic clearance suggest that in women >90% of testosterone is destroyed in the liver, while the remaining testosterone is used in target cells.[47,51] In men, the proportions are closer to 50% going to each source. In women with stigmata of hyperandrogenism, there is an increased peripheral use of testosterone relative to hepatic clearance so that the proportion going through the liver falls to 65%. Since this quantity is unchanged, it is apparent that sex steroid manufacture and skin use are increased. This phenomenon is reflected in studies that support the increased 3α adiol G levels in hirsute women.[58–60]

SUMMARY

The manufacture of sex steroids is complex. The regulation of androgens is intriguing, particularly for a hormone whose major function seems to be to grow hair in abnormal places. Androgens do have a series of well-established metabolic effects, but it is also suggested that a much more subtle series of effects maintains well-being. There is also evidence that androgens may be important in immune response to cancer, in weight control, and in the preservation of a youthful appearance.

Our understanding of androgen control and function is incomplete, but even with our limited extent of knowledge, we can understand that significant hirsutism is a symptom of an often subtle endocrinopathy and not of Western preoccupation with appearance.

It is also clear from the complexity of the androgen production, use, and metabolism that single-sample measurements of hormones fall far short of an ideal investigation of the deranged physiology.

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