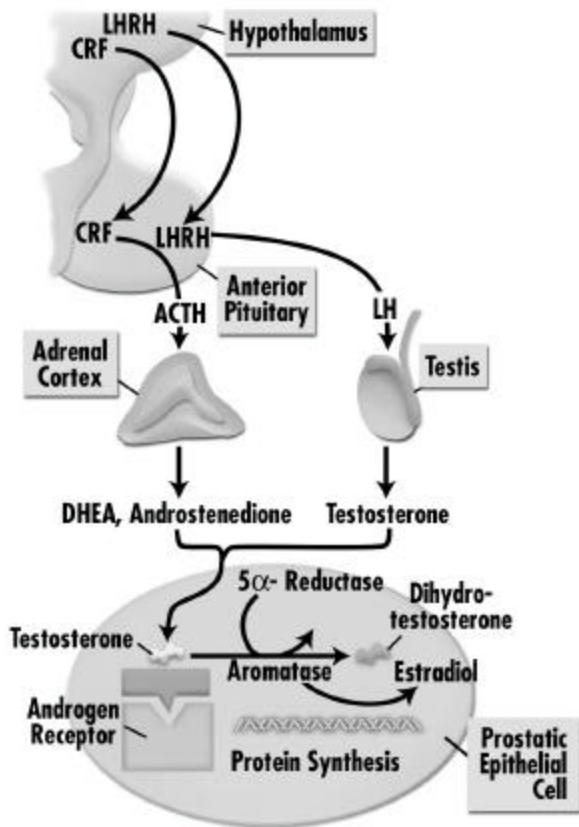


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Endocrine Aspects of Prostate Cancer

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Endocrine Aspects of Prostate Cancer



Development, growth and function of the prostate gland are under endocrine control: prostate cells have androgen receptors and depend on circulating androgens to subsist and progress. Prostate cancer develops as a result of unexplained aberrations within these cells which, at least in the early stages of the disease, continue to exhibit an exploitable androgen dependency. Consequently, prostate cancer generally responds very well to androgen deprivation therapy (ADT). This term covers a variety of treatment modalities differing from one another in their manner of intervening in the complex endocrine relationships that apply.

Accordingly, in managing prostate cancer, it is important to understand relevant aspects of the biological context, and to appreciate how laboratory measurements of endocrine-related parameters may help in evaluating and optimizing the course of androgen deprivation therapy.

The hormonal axis—a review

Testosterone is the principal androgen in circulation. The Leydig cells in the testes secrete this steroid hormone in response to stimulation from luteinizing hormone (LH, lutropin), a gonadotropin secreted by the anterior pituitary. LH secretion is influenced by the hypothalamic production of luteinizing hormone-releasing hormone (LHRH).

Testosterone, LH and LHRH constitute the elements of a negative feedback control mechanism. Low circulating testosterone levels increase the secretion of LHRH, which leads to increased production of LH and consequently to increased testosterone production as well. High testosterone levels, on the other hand, inhibit LHRH release, thus diminishing in turn both LH secretion and testosterone secretion.

LHRH is secreted by the hypothalamus in a pulsatile (intermittent) fashion and has a short half-life in circulation.¹ It acts directly on the anterior pituitary, binding specifically to membrane receptors on the surface of the gonadotropic cells. These receptors retain their activity only while intermittently occupied. It is this event, the binding of LHRH to its receptor, which triggers the secretion of LH and follicle-stimulating hormone (FSH, follitropin) as well.

Testosterone circulates for the most part bound to plasma proteins, predominantly sex hormone-binding globulin (SHBG) and albumin. Hence, measurements of total testosterone may not always provide a clinically adequate index to “free” or “bioavailable” androgen levels: the free androgen index (FAI)—essentially the ratio of total testosterone to SHBG—or some other derived measure may sometimes provide a more appropriate index.

Another complication arises from the testes not being the only source to consider. The adrenal glands also produce androgens, including androstenedione and dehydroepiandrosterone (DHEA), which normally constitute about 5 percent of the total androgen pool. These steroids act as hormones in their own right, but can also be converted to testosterone in the prostate.² The anterior pituitary’s secretion of adrenocorticotropic hormone (ACTH) stimulates the release of adrenal androgens as well as other corticosteroids. ACTH release is influenced in turn by the hypothalamic hormone corticotropin-releasing factor (CRF).

Testosterone has direct effects upon muscle mass, skeletal growth, spermatogenesis and the development of sexual organs. It also serves as a precursor to still more potent androgens. In particular, once it enters the cells of a target tissue, such as the prostate, the enzyme 5 α -reductase converts this steroid into dihydrotestosterone (DHT), while a relatively small amount of testosterone, about 1 percent, metabolizes to estradiol (E2).

DHT has effects on the prostate, sebaceous glands (loss of scalp and body hair) and the skin, whereas E2 mainly affects bone formation and breast tissue. DHT is preferentially concentrated within the prostate cell and has approximately seven times the androgenic potency of testosterone. Indeed, DHT is believed to be the primary intracellular messenger responsible for stimulating gene expression; its binding to the intracellular androgen receptor activates cellular functions within the prostate.

By attaching to the receptor, androgens initiate the synthesis of extrinsic “growth” factors. Growth factors are transported to the target organ via the bloodstream. Within the prostate cell, they can influence the production of additional growth factors, either locally (within the same cell) or remotely (by other cells). The net effect of this process is the synthesis of proteins, including prostate-specific antigen (PSA).

Effects of androgen deprivation therapy on the endocrine axis in prostate cancer

ADT involves treatments that suppress testosterone production and/or block its action at the cellular level. Table 1 lists common means of implementing ADT.

Orchiectomy, i.e. surgical castration, reduces testosterone by 90 to 95 percent within 3 to 12 hours, with the remainder being that derived from the adrenal glands. The operation results in a reactive rise in LHRH and CRF, and thus also in LH, FSH and ACTH, due to interruption of the feedback loop. In such cases, it is not uncommon for LH or FSH levels to rise to as much as 10 times the upper limit of normal.

Table 1. Common forms of androgen deprivation therapy

Orchiectomy (surgical castration)
LHRH agonists (LHRH-A)
Nonsteroidal antiandrogens
Inhibition of steroid biosynthesis
Estrogens
Progestins
Glucocorticoids
Combination treatments

When LHRH agonists (LHRH-A) are administered (medical castration), a biphasic phenomenon occurs during the first 2 to 3 weeks of continuous use. At first, LHRH receptors are stimulated by the agonist, causing a rise in both LH and testosterone levels. With continued exposure, LHRH receptors become either desensitized or down-regulated.¹ LH levels fall to undetectable levels after 3 to 4 weeks of continuous LHRH-A therapy, leading to “castrate” testosterone levels.

The low circulating testosterone levels resulting from surgical or medical castration cause CRF to be released from the hypothalamus, which stimulates ACTH production by the anterior pituitary gland. Increased ACTH levels not only induce cortisol secretion from the adrenal cortex, but also lead to increased biosynthesis of adrenal androgens, particularly androstenedione.³

Within the prostate cell, adrenal androgens are converted very efficiently into DHT by the enzyme 5 α -reductase. In men undergoing orchiectomy, therefore, postoperative intracellular DHT levels, though reduced, remain

relatively high—reportedly as high as 40 percent of preoperative levels.⁴

Potency-sparing ADT, employing a nonsteroidal antiandrogen such as bicalutamide that blocks the effects of androgens at the receptor level, is associated with a very different pattern of alterations in circulating hormone levels: this form of ADT increases the levels of LH, total and free testosterone, DHT and E2.⁵ A similar but less profound hormonal alteration occurs when 5 α -reductase inhibitors, such as finasteride, are used.⁶

ADT can also involve treatment with drugs that inhibit key enzymes involved in the stepwise biosynthesis of testosterone and DHT from cholesterol, in both the adrenal glands and testes.⁷ Aminoglutethimide (AC) and, in some cases, high-dose ketoconazole (HDK) not only decrease biosynthesis of adrenal androgens, but also block the production of cortisol and the mineralocorticoid, aldosterone.⁸

The low levels of circulating cortisol, which can sometimes be associated with symptomatic hypoadrenalism, result in a compensatory increase in ACTH. Since physiologic doses of corticosteroids block the compensatory rise in ACTH levels, these agents are commonly given in combination with AC or HDK to prevent undesirable side effects.

Conclusions

Function and growth of the prostate gland are closely regulated by feedback control mechanisms involving the hypothalamic-adrenal-gonadal axis. Prostate cancer, once it develops, largely depends on endocrine influences for its survival and possible progression. ADT is an effective means to treat early-stage prostate cancer, and can be accomplished by several methods. However, each type of ADT disrupts feedback loops in one way or another, and results in reflex increases in a variety of endocrine markers.

As a result of the side effects often observed, some clinicians elect to treat prostate cancer patients with two or more forms of ADT having different mechanisms of action. In most cases, this reduces the magnitude of the reflex disruption of endocrine feedback loops.

Clearly, then, to assess the impact of ADT, the clinician needs to follow more than just the prostate cancer patient’s PSA levels. The judicious determination of various endocrine parameters which can be readily measured by immunoassay—including testosterone, SHBG, E2, DHEA or DHEA-SO₄, LH, FSH and ACTH—can provide a useful window into the complex interplay of hormones during ADT.

References

1. Sandow J. The regulation of LHRH action at the pituitary and gonadal receptor level: a review. *Psychoneuroendocrinology* 1983;8:277-97.
2. Bélanger A, Brochu M, and Cliché J. Levels of plasma steroid glucuronides in intact and castrated men with prostatic cancer. *J Clin Endocrinol Metab* 1986;62:812-5.
3. Sciarra F, Sorcini G, Di Silvero F, Gagliardi V. Plasma testosterone and androstenedione after orchiectomy in prostatic adenocarcinoma. *Clin Endocrinol (Oxf)* 1973;2:101-9.
4. Labrie F, Dupont A, Giguere M, et al. Benefits of combination therapy with flutamide in patients relapsing after castration. *Br J Urol* 1988;61:341-6.
5. Iversen P, Melezinek I, Schmidt A. Nonsteroidal antiandrogens: a therapeutic option for patients with advanced prostate cancer who wish to retain sexual interest and function. *BJU Int* 2001 Jan;87(1):47-56.
6. Matzkin H, Chen J, Lewyshon O, Ayalon D, Braf Z. Effects of long term treatment with finasteride (MK-906), a 5-alpha reductase inhibitor, on circulating LH, FSH, prolactin and estradiol. *Horm Metab Res* 1992 Oct;24(10):498-9.
7. De Coster R, Caers I, Coene MC, et al. Effects of high dose ketoconazole therapy on the main plasma testicular and adrenal steroids in previously untreated prostatic cancer patients. *Clin Endocrinol (Oxf)* 1986;24:657-64.
8. Santen RJ, Wells SA, Runic S, et al. Adrenal suppression with aminoglutethimide. I. Differential effects of aminoglutethimide on glucocorticoid metabolism as a rationale for use of hydrocortisone. *J Clin Endocrinol Metab* 1977;45:469-79.

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