ARTICLES

Prooxidant–Antioxidant Shift Induced by Androgen Treatment of Human Prostate Carcinoma Cells

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Background: Prostate cancer is a disease associated with aging. Also commonly associated with increasing age is a shift in the prooxidant–antioxidant balance of many tissues toward a more oxidative state, i.e., increased oxidative stress. We hypothesize that androgen exposure, which has long been associated with the development of prostate cancer, may be a means by which the prooxidant–antioxidant balance of prostate cells is altered. *Purpose:* Using established prostate carcinoma cell lines, we studied the effect of androgens on various parameters of oxidative state (e.g., generation of hydrogen peroxide and hydroxyl radicals, lipid peroxidation, and oxygen consumption) and antioxidant defense mechanisms (e.g., the glutathione system and catalase). *Methods:* The androgen-responsive LNCaP and the androgen-independent DU145 prostate carcinoma cell lines were exposed to 5α-dihydrotestosterone (D^{HT}) and to the synthetic androgen R1881. The cellular proliferation responses were measured by use of a fluorometric assay to quantitate the amount of DNA. The generation of reactive oxygen species was measured by use of 2′,7′-dichlorofluorescin diacetate, a dye that fluoresces in the presence of hydrogen peroxide or hydroxyl radicals. Lipid peroxidation was quantitated by use of a chromogen specific for malonaldehyde and 4-hydroxy-2(E)-nonenal. General mitochondrial activity was determined by assaying 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) reduction. A Clark-type electrode was used to assess oxygen consumption per cell. Intracellular glutathione concentrations and the activities of catalase and γ-glutamyl transpeptidase were measured spectrophotometrically. All *P* values resulted from two-sided tests. *Results:* DHT at less than 1 to 100 n*M* (a concentration range encompassing the physiologic levels of DHT considering all ages) and R1881 at 0.1-1 n*M* concentrations were effective in inducing in LNCaP cells comparable proliferative responses and changes in oxidative stress. In contrast, neither DHT nor R1881 had any effect on the oxidative stress in DU145 cells. The mitochondrial activity in LNCaP cells, as measured by MTT reduction, was significantly elevated above the levels of the untreated controls by DHT (0.1-1000 n*M*) and R1881 (0.05-1 n*M*) ($P<.001$ in both). Oxygen consumption and catalase activity were increased in LNCaP cells in the presence of 1 n*M* R1881 by 60% and 40%, respectively, over the values in the untreated control cells ($P<.03$ and $P<.01$, respectively). The same concentration of R1881 resulted in a decrease in intracellular glutathione concentrations and an increase in γ-glutamyl transpeptidase activity in LNCaP cells. Treatment with the oxidizing agents H_2O_2 and menadione produced an increase in γ-glutamyl transpeptidase activity in LNCaP cells, whereas treatment with the antioxidant compound ascorbic acid (100 m*M*) reduced the oxidative stress produced in LNCaP cells by 1 n*M* R1881 and completely blocked the γ-glutamyl transpeptidase activity. *Conclusions:* Physiologic levels of androgens are capable of increasing oxidative stress in androgen-responsive LNCaP prostate carcinoma cells. The evidence suggests that this result is due in part to increased mitochondrial activity. Androgens also alter intracellular glutathione levels and the activity of certain detoxification enzymes, such as γ-glutamyl transpeptidase, that are important for maintenance of the cellular prooxidant–antioxidant balance. [J Natl Cancer Inst 1997;89:40-8]

Prostate cancer is the most commonly diagnosed solid tumor in U.S. men (*1*). It is associated with aging and occurs in a latent or in a clinical form in 30%-40% of men by age 30-50 years and increases to 75% in men by age 80 (*2,3*). The cause of this disease is not well understood; however, certain factors are commonly linked to its development. These factors include genetic predisposition and exposure to androgens and other hormones, infectious agents, and environmental and dietary factors (*2*). The importance of androgens in prostate carcinogenesis is suggested by the observations that prostate cancer rarely occurs in eunuchs or men with a deficiency in 5α-reductase, the enzyme responsible for converting testosterone to its more active form, 5α-dihydrotestosterone (DHT) (*2,3*). Normal prostate development and functional maintenance depend on androgens, and at least 75% of tumors in men with metastatic prostate cancer are androgen dependent at initial diagnosis (*3,4*).

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See "Notes" section following "References."

Prostate Cancer Screening 'Not for All'

MARCH 18, '97 *Washington Post Service* (P.2) *

WASHINGTON — The American College of Physicians, in a break with what has become a widespread practice, has concluded that there is no evidence that patients benefit from routine screening for prostate cancer and recommends against regular testing for all men.

''Screening for prostate cancer is not for everyone,'' said Harold Sox Jr., the group's president-elect designate.

Because of uncertainties in the reliability of the tests, and the risks of aggressive early treatment, the organization decided screening should be undertaken as an ''individualized decision'' of each patient following counseling by physicians.

The new guidelines, published in the new issue of the Annals of Internal Medicine, are at odds with recommendations of the American Cancer Society and other medical groups.

The American Cancer Society, the American College of Radiology and the American Urological Association recommend that men begin undergoing annual digital exams at age 40. The cancer society recommends also getting annual prostate-specific antigen tests beginning at age 50.)-PSA

But the American College of Physicians, in its first set of recommendations on the issue, advises that ''rather than screening all men for prostate cancer as a matter of routine, physicians should describe the potential benefits and known harms of screening, diagnosis and treatment, listen to the patient's concerns, and then individualize the decision to screen.'' The group comprises 100,000 specialists in internal medicine.

PSA テストは uncertainty in reliability がおおようです。

aggresive early treatment のもたらす risk がおおようです。

* P.2.; 科学誌ではなく、一般の米国内のニュース。