Regulation of the gap junction connexin 43 gene by androgens in the prostate

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ABSTRACT

Androgens play an important role in prostate gland development and function, and have been implicated in prostate carcinogenesis. We report the regulation of the gap junctional intercellular communication gene connexin 43 (Cx43) by androgens in the prostate gland. In rat ventral prostate tissue, only trace levels of Cx43 mRNA were detected. Castration, however, resulted in a high increase in Cx43 mRNA and protein. Cx32 was unchanged. Castration-induced Cx43 mRNA and protein were abolished by administration of dihydrotestosterone (DHT). Following castration, prostate weights were approximately 16% of sham-treated controls. However, DHT replacement resulted in prostate weights which were not different from sham-treated controls. Under similar castration conditions, Cx43 induction coincided with pronounced apoptosis in the prostate gland cells, and DHT prevented the induction of apoptosis. Given the physiological role of gap junctions and androgens in the regulation of prostate tissue homeostasis, our observations are relevant to the understanding of androgen-dependent prostate carcinogenesis.

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INTRODUCTION

Prostate cancer is amongst the most common cancers diagnosed in men. Although causal factors are not fully understood, there is mounting evidence that androgens, which play an important physiological role in normal prostate tissues, are implicated in prostate carcinogenesis (reviewed by Aquilina et al. 1997). This is based on earlier observations showing a low incidence of prostate cancer in castrated men (Wilding 1995), and in individuals with inherent deficiency in 5α-reductase (Imperato-McGinley et al. 1974), an enzyme that converts testosterone to dihydrotestosterone (DHT) with a high affinity for androgen receptor. In laboratory animals, androgen deprivation or inhibition of 5α-reductase inhibits cell proliferation of the androgen-responsive prostatic carcinoma R-3327 (Brooks et al. 1991). Moreover, strategies to deplete or decrease androgen levels have emerged as a
palliative treatment for both benign and malignant prostate cancer (Soloway & Matzkin 1993, Aquilina et al. 1997).

Molecular mechanisms by which androgens promote prostate cancer growth are not fully understood. Androgens have been reported to stimulate the expression of several regulatory proteins, including the prostastic binding protein also called prostatein (Vercaeren et al. 1992), cystatin-related protein (Winderickx et al. 1990) and proliferating cell nuclear antigen (Perry & Tindall 1996). Androgens also induce stimulation of neutral lipid synthesis, including triglyceride and cholesterol esters in the prostate gland (Swinnen et al. 1990). Androgens prevent apoptosis in normal prostate epithelial cells, while androgen ablation following castration results in inhibition of cell proliferation and activation of apoptosis of androgen-dependent prostatic glandular epithelial cells (Kyprianou et al. 1990). More recently, it has been reported that androgen deprivation in androgen-dependent tumor can mediate apoptosis via modulation of insulin-like growth factor-binding proteins (IGFBP) (Nickerson et al. 1999). Although the contribution of these androgen-associated mechanisms to prostate carcinogenesis has yet to be proven, they suggest that androgens exert a multifactorial mechanism that regulates the balance between cell proliferation, differentiation, and likely apoptosis.

Hormones such as estrogens and androgens regulate a variety of tissues and cell-specific genes that have been associated with cancer. These include connexins (Cx), a family of at least 13 genes that mediate the formation of gap junctional intercellular communication (GJIC). GJIC plays a role in the regulation of tissue homeostasis including cell proliferation and differentiation (reviewed by Fishman et al. 1991, Bruzzone et al. 1996, Goodenough et al. 1996, Kumar & Gilula 1996). Cx32, Cx40, and/or Cx43 have been identified as major constituents of GJIC in prostate tissue and/or primary prostate epithelial cells (Meda et al. 1993, Mehta et al. 1996, 1999, Hossain et al. 1999). Cx43 is essential for survival (Reaume et al. 1995), and is assembled into channels that allow for GJIC (Loewenstein 1981). Several growth factors, protein kinases, secondary messengers including cAMP, and oncogenes such as ras, neu and src (Madhukar et al. 1989, Crow et al. 1990, Lau et al. 1992, 1996, Atkinson et al. 1995) tightly regulate GJIC. Furthermore, hormones including estrogens, progesterone, gonadotropins, and parathyroid hormone (Schiller et al. 1992, Lye et al. 1993, Petrocelli & Lye 1993, Monaghan et al. 1994, Hendrix et al. 1995, Lefebvre et al. 1995, Ou et al. 1997, Khan-Dawood et al. 1998, Murray & Shah 1998) also regulate GJIC.

In this study, we have examined the effect of androgens on Cx43 in the rat prostate. We provide evidence that androgens regulate the expression of the Cx43 gene in prostate tissue from normal and castrated rats. We have demonstrated that castration is associated with a dramatic increase in Cx43 mRNA and protein expression, and this coincides with induction of apoptosis. Treatment with testosterone or DHT abolished castration-induced Cx43 expression, and prevented apoptosis. Given the physiological role of gap junctions in the regulation of prostate tissue homeostasis, these observations may have a broad implication for the understanding of androgen-dependent prostate carcinogenesis.

MATERIALS AND METHODS

Animal treatment and prostate tissue preparation

Male Sprague–Dawley rats (10 weeks old; 230–250 g) were purchased from Charles River Laboratories (Montreal, Quebec, Canada). Animals were maintained and treated according to the guidelines of the Canadian Council on Animal Care. McGill Animal Care Committee approved this experimental protocol. Castration was performed via the scrotal route under ketamine/xylazine anesthesia. To study the long-term effect of androgen replacement on Cx43 gene expression, groups of castrated rats were implanted subcutaneously at the time of castration with 0·5, 1·0 or 2·0 cm silastic tubes (0·1 cm internal diameter; Dow Corning, Midland, MI, USA) containing testosterone or 5α-DHT via mid-scapular incision. Control castrated rats experienced the same surgical implantation with empty silastic tubes. The released rate of androgens from silastic implants was 1·2 µg/cm per day (van Steenbrugge et al. 1984). Animals were killed by 15 days after implantation. In androgen supplementation experiments, castrated rats were given daily subcutaneous injections of DHT (3 µg/kg body weight), which was freshly prepared by diluting a stock solution of 3 mg/ml in 100% ethanol in phosphate-buffered saline (PBS), beginning at the time of castration. Control castrated rats were injected with PBS only. Animals were killed after 6, 24, 48, and 72 h. The ventral prostate of each animal was excised, trimmed, weighed and frozen in liquid nitrogen, and stored at −70°C for RNA extraction and Western blot analysis.
RNA extraction and hybridization

Total RNA was isolated from the ventral prostate using RNAZol premix solution and RNAzol B method (Tel-Test, Friendswood, TX, USA). RNA from the ventral prostate of individual animals from each experimental condition (n=8) was used to examine connexin expression by Northern blot analysis as described earlier (Schechter et al. 1993). Total RNA (40 µg) was used per lane. The blots were hybridized overnight with nick-translated 32P-labeled full length Cx43 cDNA (kindly provided by Dr G I Fishman, Albert Einstein College of Medicine, Bronx, NY, USA), an EcoRI/XaoI fragment of Cx26 cDNA, or KpnI/BamH1 Cx32 cDNA (both cDNAs were kindly provided by Dr C Naus, University of Western Ontario, London, Ontario, Canada). To control for equal loading of wells, we compared total amounts of RNA present in different lanes with human glyceraldehyde-6-phosphate dehydrogenase (GAPDH) cDNA. Quantitative analysis of gene expression was accomplished by densitometry scans of autoradiograms. Results are plotted as the average of eight individual animals ± S.E.M.

Western blot analysis

Ventral prostate tissue from individual animals was homogenized in homogenization buffer (20 mM Tris–HCl, pH 7.5, 1% Triton X-100, 100 mM NaCl, 50 mM NaF, 2 mM phenyl-methyl sulfonyl-fluoride and 0.5% Nonidet P-40). The lysate was clarified by centrifugation at 14 000 g for 15 min. The samples were analyzed for protein content by the Bradford method (Bio-Rad Laboratories, Hercules, CA, USA). Protein (50 µg) was electrophoresed on 12% SDS-PAGE using the Protein II system (Bio-Rad Laboratories) and transferred to a nitrocellulose membrane as described (Schecter et al. 1993). The blots were blocked with 5% skim milk in TBS (25 mM Tris–HCl, pH 7.6, 500 mM NaCl) for 2 h at room temperature and incubated with 1:500 dilution of a mouse monoclonal anti-Cx43 antibody, which recognizes a cytoplasmic domain of rat Cx43 (Zymed Laboratories Inc., San Francisco, CA, USA) in TBST (TBS containing 0.1% Tween-20) for 3 h. After extensive washing in TBST, the filters were incubated for 1 h in a horseradish peroxidase-conjugated anti-mouse antiserum (1:2500 dilution; Amersham, Oakville, Ontario, Canada). Filters were washed three times with TBST and once with TBS before Western blots were visualized by a chemiluminescence-based photoblot system (ECL; Amersham). Membranes were stripped, and then probed with a monoclonal antibody that recognizes α-tubulin or GAPDH (ICN, Mississauga, Ontario, Canada). Both of these housekeeping genes, used as internal controls, were not affected by androgens (data not shown). Results are plotted as the average of eight individual animals ± S.E.M.

RESULTS

Figure 1 summarizes the effect of castration on Cx43 and Cx32 mRNA expression. Northern blot analysis revealed that rat prostate tissue expressed a very low level of Cx43 mRNA. Castration, however, resulted in a dramatic increase in Cx43 mRNA in the ventral prostate (Fig. 1A and B). Cx43 mRNA increased 2-fold by 6 h and reached 16-fold by 100 h following castration. Cx43 mRNA levels were significantly different from controls at all time-points (P<0.01) as determined by Mann–Whitney U test. Castration-induced Cx43 mRNA was abolished by daily administration of DHT given at a dose of 3 µg/kg body weight per day (Fig. 1A and B). Under this condition, Cx43 mRNA dropped to trace levels between 48 and 72 h after castration (Fig. 1B). In contrast to Cx43, Cx32 mRNA was not affected by castration or DHT treatment (Fig. 1C and D). Cx26 mRNA was not detected by Northern blot analysis (data not shown).

Continuous androgen replacement by implanting silastic tubes, containing either testosterone or DHT, following castration resulted in prostate weights which were not significantly different from sham-castrated controls (Fig. 2, lane I versus others animals which received increasing doses of testosterone or DHT ranging from 0·6 to 2·4 µg/cm per
day). However, the prostate weights of castrated rats were approximately 16% of sham-treated control rats (Fig. 2, lane C).

Cx43 mRNA level was approximately tenfold higher in prostates from castrated rats (Fig. 3, lane C) as compared with sham-treated controls from resting rats (Fig. 3, lane I). However, Cx43 mRNA levels returned to normal levels following androgen replacement using doses of 0.6 to 2.4 µg/cm per day for 15 days (Fig. 3). Compared with sham-castrated rats (Fig. 4, lane I), castration resulted in a significant induction of Cx43 protein level (Fig. 4, lane C). At equal molar concentration, testosterone was consistently found to be slightly less potent than DHT at suppressing castration-induced Cx43 protein expression (Fig. 4).

In prostate tissue, castration is associated with the activation of an apoptotic program that affects primarily glandular epithelial cells. To examine the association between Cx43 regulation and the apoptosis process in the ventral prostate after hormone ablation, we examined the occurrence of TUNEL-labeled nuclei of prostate glandular epithelial cells. In control tissue, no significant staining was observed (Fig. 5A). However, the incidence of TUNEL-labeled nuclei was significantly elevated 24 h (Fig. 5B) and 48 h (Fig. 5D) post-castration when compared with control tissues (Fig. 5A). Treatment with DHT at a dose of 3 µg/day for 2 days (48 h post-castration) reduced the incidence of TUNEL-labeled nuclei (Fig. 5C) compared with untreated castrated rats (Fig. 5D).
DISCUSSION

Several studies have shown that hormones, including estrogens, progesterone and thyroid hormones (Schiller et al. 1992, Lye et al. 1993, Petrocelli & Lye 1993, Monaghan et al. 1994, Hendrix et al. 1995, Lefebvre et al. 1995, Risek et al. 1995, Cyr et al. 1996, Stock et al. 1998) regulate GJIC and Cx. In myometrium, estrogens up-regulate the expression of Cx43 mRNA while progesterone antagonizes this increase (Lye et al. 1993). Also, estrogens induce transcriptional activation of Cx43 (Hendrix et al. 1995, Risek et al. 1995). Upstream of the non-coding region of the Cx43 gene has revealed potential putative estrogen-responsive elements as well as AP1 and AP2 elements (Yu et al. 1994). AP1, a cell cycle-dependent transcriptional complex, has been shown to antagonize transcriptional activation of retinoid- and glucocorticoid-responsive genes (Nicholson et al. 1990). Cyr et al. (1996) previously showed that the epididymis from orchidectomized rats had increased Cx43 expression and regional changes in the expression pattern of Cx43, suggesting that androgens regulate Cx43 in this organ. However, the effect of castration and sustained release of androgens on prostate weight. Rats were castrated and given DHT daily as described in Materials and Methods. Prostate weights of eight animals per group were plotted as means ± s.e.m. Treatment groups include: sham-castrated rats (I; lane 1); 15 days after castration (C; lane 2); castration combined with 0·5 cm (lane 3), 1·0 cm (lane 4), or 2·0 cm (lane 5); testosterone (T) silastic implantation for 15 days and castration combined with 15 days implantation of 0·5 cm (lane 6), 1·0 cm (lane 7), or 2·0 cm (lane 8) DHT silastic tubes. Prostate weight of sham-castrated rats (lane 1) was not significantly different from androgen-replaced groups (lanes 3–8) (P<0·01) as determined by Mann–Whitney U test.

FIGURE 2. Effects of castration and sustained release of androgens on prostate weight. Rats were castrated and given DHT daily as described in Materials and Methods. Prostate weights of eight animals per group were plotted as means ± s.e.m. Treatment groups include: sham-castrated rats (I; lane 1); 15 days after castration (C; lane 2); castration combined with 0·5 cm (lane 3), 1·0 cm (lane 4), or 2·0 cm (lane 5); testosterone (T) silastic implantation for 15 days and castration combined with 15 days implantation of 0·5 cm (lane 6), 1·0 cm (lane 7), or 2·0 cm (lane 8) DHT silastic tubes. Prostate weight of sham-castrated rats (lane 1) was not significantly different from androgen-replaced groups (lanes 3–8) (P<0·01) as determined by Mann–Whitney U test.

FIGURE 3. Effects of castration and androgen replacement on Cx43 mRNA expression. Rats were castrated and treated with the testosterone (T) or DHT for 15 days as indicated in Fig. 2. Total RNA was extracted from the prostate tissue and used for Northern blot analysis. Blots were hybridized with Cx43 or GAPDH cDNA. Gene expression was quantified by densitometric scanning of autoradiograms. (A) A representative autoradiogram of Northern blot analysis for Cx43 mRNA. (B) This represents the average ratios (± s.e.m.) of Cx43 mRNA to GAPDH mRNA from eight individual rats, expressed as arbitrary density units (ADU). Lane C refers to control prostate tissue from 15-day castrated rats. Lane I corresponds to sham-castrated prostate, and lane C corresponds to prostate tissue from 15-day castrated rats (n=8). Lane +ve corresponds to a positive control using total RNA from the breast cancer cell line Hs578T that expresses high levels of Cx43 (Laird et al. 1999). Cx43 mRNA levels in castrated prostate were significantly different from sham-castrated and androgen-replaced groups (P<0·01), as determined by Mann–Whitney U test. No significant difference was observed between sham-castrated and androgen-replaced groups.
androgens on Cx43 gene regulation in the prostate is unclear.

The androgen receptor is a transcription factor that functions primarily via interaction with androgen-responsive elements in the promoter regions of target genes (reviewed by Beato et al. 1996, Beato & Sanchez-Pacheco 1996). We report herein the effect of androgens on Cx43 regulation in the prostate. Northern blot analysis revealed that Cx32 was highly expressed while only a weak Cx43 signal was seen in control rat prostate glands. The low expression of Cx43 was confirmed by Western blot analysis when gels were loaded with 50 µg total cellular protein. Cx43 mRNA expression was not detected by Meda et al. (1993) in rat prostate tissue. This discrepancy may be related to the fact that we loaded eight times more total RNA from whole rat ventral prostate glands on our gels for our Northern blot analysis, possibly increasing the sensitivity of our screen. Mehta et al. (1999) failed to detect Cx43 in resting adult human prostate glands but did observe Cx43 in juvenile prostates and in transformed prostate cells. Together, these results would suggest that there is little Cx43 expressed in the adult prostate gland in vivo but up-regulation of Cx43 may occur in young animals or during early stages of prostate epithelial cell transformation. However, we found that Cx43 is abundant in human normal primary prostate cells (our unpublished data), in agreement with a recent study by Hossain et al. (1999).

We have examined the effect of androgen replacement on the expression of the two prostatic gap junction proteins, Cx43 and Cx32, following removal of the testicles in the rat. Castration induced a dramatic decrease in prostate weight, while replacement of androgen, by chronic administration of testosterone or DHT to the castrated rats, prevented the decrease in ventral prostate mass. DHT was only slightly more potent than testosterone in regulating Cx43 expression, possibly due to the high affinity of DHT to androgen receptors in comparison with testosterone. Cx43 mRNA expression was dramatically up-regulated in the prostate gland of castrated rats. This castration-induced increase in Cx43 expression was completely inhibited by testosterone or DHT treatment, indicating that Cx43 expression is tightly regulated by androgens in vivo, and Cx expression is negatively correlated with proliferation.

While variation in the ratio of Cx43 between basal and epithelial cells could contribute in part to differences in total Cx43 expression between castrated versus non-castrated prostate tissue, it is unlikely that this can explain the dramatic changes in Cx43 mRNA/protein observed in our study. There is no evidence in the literature that castration could result in epithelial/basal cell ratio change that could account for the change in Cx43 expression. Furthermore, in a related study no change in epithelial/basal cell ratio was noted as a result of castration (Cyr et al. 1996). The fact that Cx32 was not affected by androgens suggests that Cx43 may mediate some of the critical aspects of prostate epithelial cell survival and proliferation. A similar study in the endometrium indicates that estrogen and progesterone regulate Cx26 and Cx43 but not Cx32 (Grummer et al. 1999). While the reported Cx43 regulation by estrogens is not surprising as Cx43 promoter contains a series of half-palindromic...

**FIGURE 4.** Effects of castration and androgen replacement on Cx43 protein levels. Rats were castrated and given various doses of either testosterone (T) or DHT as described in Fig. 3. Lane I corresponds to sham-castrated prostate, and lane C corresponds to 15-day castrated prostate tissue. Western blot analysis of individual prostate homogenate was performed as described in Materials and Methods. (A) Filters were blotted with anti-Cx43 antibody; membranes were stripped, and then probed with anti-tubulin. (B) Cx43 levels were quantified by densitometry scanning of autoradiograms and results are expressed as arbitrary density units (ADU), and presented as means ± s.e.m. (n=8).
estrogen-responsive elements (De Leon et al. 1994, Yu et al. 1994), the mechanism(s) by which DHT regulates Cx43 is still unknown. Both transcriptional and post-translational mechanisms may be involved in androgen-mediated gene regulation (Murtha et al. 1997, Perry & Tindall 1996, Vercaeren et al. 1996). In this study, we observed that castration-induced changes in prostatic Cx43 mRNA levels were more dramatic than changes in Cx43 protein, supporting the idea that both transcriptional and translational regulation of Cx43 by androgens may take place in prostate tissue. Although no androgen-responsive element has been identified in the Cx43 gene, the Cx43 promoter does contain several AP, cAMP and Sp sites, which in other promoters have been shown to interact with hormone receptors, including androgen receptor, and activate transcription (Krishnan et al. 1994, Umayahara et al. 1994, Schanke et al. 1998). This transcriptional regulation also accounts for androgen-mediated transcriptional regulation of certain prostate-specific proteins such as prostate-specific glandular kallikreins (Young et al. 1992, Murtha et al. 1997). Post-transcriptional regulation of Cx43 involves mainly Cx43 phosphorylation by protein kinase C, mitogen-activated protein kinase and src tyrosine protein kinase (Musil et al. 1990, Musil & Goodenough 1991, Lau et al. 1992, 1996, Laird et al. 1995). Therefore, the effect of androgen on these Cx43 regulatory mechanisms remains to be explored.

FIGURE 5. In situ localization of TUNEL-labeled cells in the rat ventral prostate from control and castrated rats. Frozen tissue sections from ventral prostate of control and castrated rats were immunostained using the TUNEL method to identify cells undergoing apoptosis, as described in Materials and Methods. The sections consist of prostate epithelium (e) around glandular lumen (l), and delicate stroma with occasional capillaries (c) containing red blood cells. The figure is a representative result of the TUNEL assay in prostate tissues (n=5). (A) This corresponds to control prostate gland and (B) and (D) show the occurrence of apoptosis in prostate epithelium (arrow) from 24 h and 48 h post-castration respectively. (C) This shows reduction of apoptosis in prostate gland from 48 h post-castration supplemented with 3 µg DHT per day. Magnification × 100.
The prostate gland is tightly dependent on androgens for its development. It is composed of heterogeneous populations of epithelial cells, fibroblasts, smooth muscle cells, and endothelial cells. Following castration, testosterone concentration drops rapidly, resulting in severe regression of the prostate. This regression is due to the activation of an apoptotic program that mainly affects glandular epithelial cells. Several earlier studies have shown an inverse correlation between cell proliferation and Cx43 expression (Naus et al. 1992). In the rat model, organ homeostasis in the ventral prostate is achieved by balancing two distinct processes, one responsible for initiation of DNA synthesis and cell proliferation and the other responsible for inhibiting apoptosis. Both of these processes are thought to be under androgenic control (Kyprianou et al. 1990, Aquilina et al. 1997, Nickerson et al. 1999). Apoptosis of prostatic glandular epithelial cells involves cell–cell and cell–matrix interaction. In rats, hormone withdrawal induces apoptosis as the secretory epithelial cells are localized in the distal and intermediate regions of the ducts, and are dependent on androgens for survival (Columbel & Buttyan 1995).

Several extracellular proteases including metalloproteinases 2 and 9 (Lokeshwar et al. 1993), and cathepsin B and D (Gu et al. 1994, Guenette et al. 1994) are induced during prostate regression. Castration also induces expression of transforming growth factor-β1 (TGFβ1) in stromal (Kyprianou et al. 1994) and type-I and type-II TGFβ receptors in epithelial cell (Kim et al. 1996), and IGFBP-5 (Nickerson et al. 1999). In our study, we have demonstrated that shortly after castration-induced androgen deprivation, Cx43 gene expression induction coincides with the rapid death of prostatic cells, in agreement with other studies (Nickerson et al. 1998). Furthermore, prevention of castration-induced prostate regression by androgens is associated with suppression of Cx43 expression. These observations suggest that Cx43 and perhaps other connexins may participate in prostate involution. Trosko and colleagues were the first to hypothesize that gap junctions may play a role in apoptosis (reviewed by Trosko & Inoue 1997). This hypothesis is now supported by recent studies showing that Cx43 expression increases in response to cellular injury (Lin et al. 1998) and inflammation (Fernandezk-Cobo et al. 1998).

The connection between androgens and Cx43 expression is significant since androgens are linked to the growth of normal prostate, as well as the development of benign prostate hyperplasia and prostate cancer (Soloway & Matzkin 1993, reviewed by Aquilina et al. 1997). Androgens act to promote cell growth. Reduced Cx and GJIC have been associated with increased cell growth (Loewenstein & Rose 1992, Yamasaki & Naus 1996), while enhancement of Cx expression and GJIC inhibit cellular growth in vitro and in vivo (Mehta et al. 1989, 1999, Zhu et al. 1991) and suppress malignant transformation (Loewenstein & Rose 1992). Our observations suggest that pharmacological strategies that up-regulate Cx43 may be useful in treatment and/or prevention of prostate cancer. Several agents such as diethylstilbestrol (Thompson 1995), luteinizing hormone-releasing hormone analogues (Aquilina et al. 1997), finasteride (Boyle et al. 1996), and non-steroidal anti-androgens (flutamide, bicalutamide) (Labrie et al. 1993, Soloway & Matzkin 1993) are used either singly or in combination in the management of prostate cancer. These compounds have been shown to disrupt or decrease androgen levels, and it will be interesting to determine if these compounds also up-regulate Cx43.

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