

THE ALPHA1-ADRENOCEPTOR ANTAGONIST PRAZOSIN RADIOSENSITISES HYPOXIC PROSTATE CANCER CELLS

Hypothesis / aims of study

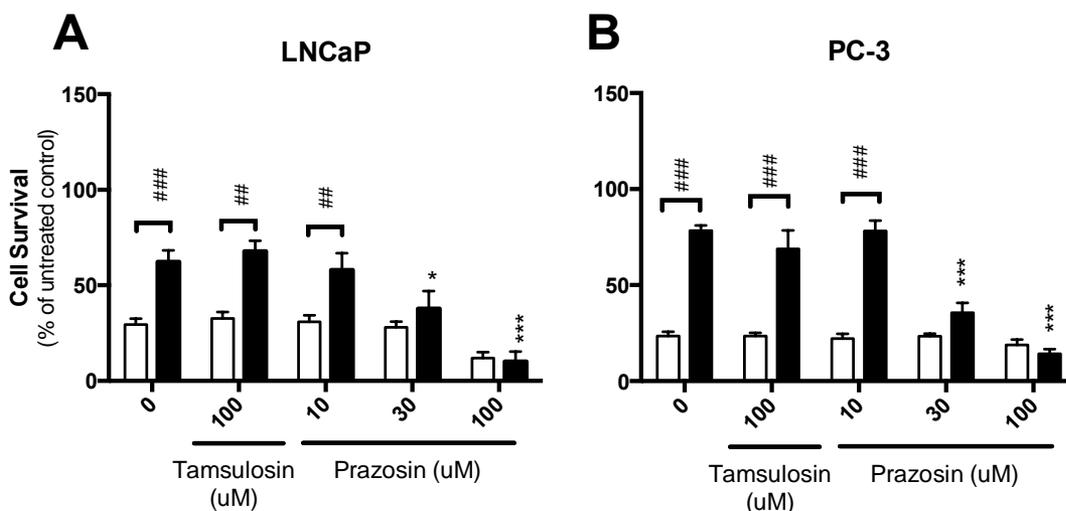
Acute lower urinary tract symptoms (LUTS) are commonly experienced by men treated with radiotherapy for localized prostate cancer. Alpha₁-adrenoceptor antagonists are known to improve radiation-induced voiding and continence LUTS. Additionally, some of these drugs, such as prazosin, have been reported to increase apoptosis of the prostate and reduce the incidence of prostate cancer compared to unexposed men [1, 2]. Furthermore, pre-clinical models demonstrate cytotoxic actions of these drugs in prostate cancer cell lines, which occur via alpha₁-receptor independent mechanisms [3]. The dual LUTS- and cancer-targeting actions of these antagonists may be beneficial for patients undergoing radiotherapy for localised prostate cancer. Therefore, the overall aim of this study was to investigate the potential radiosensitising actions of the alpha₁-adrenoceptor antagonist, prazosin, in irradiated prostate cancer cells.

Study design, materials and methods

Human castration-sensitive LNCaP and castration-resistant PC-3 prostate cancer cells were treated acutely (2 h) with prazosin or tamsulosin (0 – 100 µM) and irradiated (6 MV, 5 Gy) under normoxic or hypoxic conditions. Tumour hypoxia is an important aspect of solid tumour physiology, which promotes tumourigenesis and radioresistance. Hypoxia (< 0.2% oxygen in culture medium) was generated by purging controlled-atmosphere chambers containing cells with oxygen-free nitrogen for 38 minutes. Following acute prazosin treatment, cells were washed and incubated in drug-free medium for 5 days then cell survival was measured using a resazurin reduction assay.

Results

Under normoxic conditions, irradiation resulted in approximately 70.6% and 76.3% reduction in LNCaP and PC-3 survival, respectively (Figure 1). The presence of prazosin (10-100 µM) or tamsulosin (100 µM) during irradiation had no significant effect on normoxic cell survival. In contrast, hypoxia protected LNCaP and PC-3 cells from irradiation-induced cytotoxicity, with an approximately 2- to 3-fold increase in cell survival compared to normoxic cells, respectively (###P<0.001, Figure 1A, B). Prazosin, but not tamsulosin, increased sensitivity of hypoxic prostate cancer cells to irradiation in a concentration-dependent manner, with 30 and 100 µM prazosin reducing cell survival (*P<0.05, ***P<0.001, n=5) to that of irradiated normoxic cells (P>0.05 [n=5] for comparison of irradiated normoxic vs. irradiated hypoxic cells).



Interpretation of results

Prazosin has cytotoxic actions on prostate cancer cells, which are enhanced in the presence of hypoxia. Prazosin completely abolished hypoxia-mediated radioresistance in PC-3 and LNCaP cells. In contrast, tamsulosin did not affect prostate cancer cell survival in any of the conditions tested.

Concluding message

These novel findings suggest prazosin may be useful to overcome radioresistance of prostate tumours while improving acute LUTS associated with radiotherapy for localised prostate cancer.

References

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3. Benning CM1, Kyprianou N. Quinazoline-derived alpha1-adrenoceptor antagonists induce prostate cancer cell apoptosis via an alpha1-adrenoceptor-independent action. Cancer Res. 2002 Jan 15;62(2):597-602

Disclosures

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