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RELATIVE CYTOTOXIC POTENCIES OF ALPHA1-ADRENOCEPTOR ANTAGONISTS IN HUMAN STROMAL AND EPITHELIAL CELL LINES

Hypothesis / aims of study

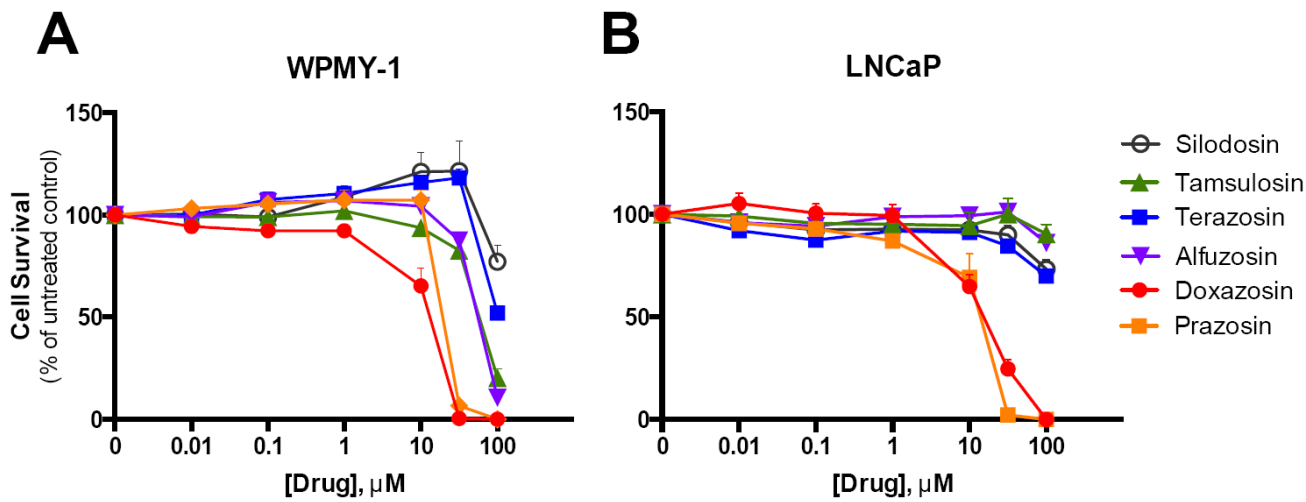
Alpha$_1$-adrenoceptor antagonists are used to treat lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). These antagonists improve urodynamic symptoms by relaxing prostate contraction via alpha$_1$-adrenoceptor receptor blockade. However, these antagonists may also act to reduce the size of the diseased prostate by increasing prostatic apoptosis [1]. The aim of this study was to assess the relative cytotoxic potencies and cell death mechanisms (apoptosis and autophagy) of various alpha$_1$-adrenoceptor antagonists in prostate cell lines.

Study design, materials and methods

Human stromal myofibroblast WPMY-1 and epithelial androgen receptor positive LNCaP prostate cells were exposed to tamsulosin, silodosin, alfuzosin, terazosin, doxazosin, prazosin (0.01 – 100 μM) or vehicle for 24 – 72 h. Resazurin reduction assay was used as an indicator of cell viability. Apoptosis and autophagy were measured using commercially available caspase-3 activity and CytoID autophagy detection kits, respectively. An autophagy inhibitor, 3-methyladenine (5 mM), was used to determine the contribution of autophagy to alpha$_1$-adrenoceptor antagonist-induced toxicity.

Results

Alpha$_1$-adrenoceptor antagonist cytotoxic potency was found to be time- and cell type-dependent. Following 72 h continuous treatment, the most potent cytotoxic drug was doxazosin in WPMY-1 (IC_{50} 11.3 μM [95% CI = 7.8-16.3]) and prazosin in LNCaP (IC_{50} 13 μM [21.0-25.7]) (Figure 1). Additionally, both doxazosin and prazosin (100 μM) were able to completely abolish survival of both cell lines ($P<0.001$, n=6). Alfuzosin, tamsulosin, and terazosin (100 μM) resulted in significant reduction (>50%) of WPMY-1 survival ($P<0.001$, n=6) (Figure 1A), where as alfuzosin and tamsulosin had no significant effect on LNCaP survival (Figure 1B). At the highest concentration (100 μM), silodosin was only able to induce modest toxicity (approximately 23% reduction in survival) in both cell lines ($P<0.05$, n=6). In WPMY-1 cells, the relative cytotoxic potency was found to be: doxazosin > prazosin = alfuzosin = tamsulosin > terazosin = silodosin and in LNCaP cells: prazosin = doxazosin > terazosin = silodosin > alfuzosin = tamsulosin (Figure 1). In LNCaP cells, only doxazosin and prazosin (30 – 100 μM) were able to increase apoptosis-related caspase-3 and autophagic activity ($P<0.01$, n=3). Furthermore, inhibition of autophagy decreased LNCaP survival ($P<0.001$, n=3) and enhanced caspase-3 activity ($P<0.01$, n=3). Likewise, autophagy inhibition enhanced prazosin-induced toxicity and apoptosis of LNCaP cells ($P<0.001$, n=3).



Interpretation of results

The relative cytotoxic potencies of alpha$_1$-adrenoceptor antagonists was found to be cell type-dependent, with doxazosin and prazosin being the most potent in WPMY-1 and LNCaP cells, respectively. Interestingly, alfuzosin and tamsulosin were significantly more potent in the stromal WPMY-1 cells, than LNCaP epithelial cells. Overall, WPMY-1 cells were found to be more sensitive to alpha$_1$-adrenoceptor antagonist-induced toxicity than LNCaP cells. While prazosin and doxaozisn were found to induce both apoptosis and autophagy in LNCaP cells, it appears apoptosis is the primary cell death mechanism contributing to alpha$_1$-adrenoceptor antagonist toxicity.

Concluding message

Alpha$_1$-adrenoceptor antagonists such as doxazosin or prazosin, which have cytotoxic effects in both epithelial and stromal cells, may prove particularly beneficial in improving LUTS associated with BPH. These drugs may have dual actions on the benign diseased prostate; relaxing prostatic contraction via alpha$_1$-receptor blockade and by reducing prostate size through apoptotic cell death mechanisms.

References

1. Kyprianou N, Litvak JP, Borkowski A, Alexander R, Jacobs SC. Induction of prostate apoptosis by doxazosin in benign prostatic hyperplasia. J Urol. 1998 Jun;159(6):1810-5.

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