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Similarities and differences between effects of angiotensin III and angiotensin II on human prostate cancer cell migration and proliferation

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ABSTRACT

Proliferation plays a critical role in tumor growth when cell migration is essential to invasion. The effect of Ang III and Ang II was evaluated on these important processes. Changes in the migration potential of prostate cancer cells were investigated using Wound Healing Test and a Transwell Migration Chamber with a 3 μm pore size. Cell proliferation was measured with a BrdU Assay and Countess Automated Cell Counter, thus determining the influence of angiotensins on hormone-dependent (LNCaP) and hormone-independent (DU-145) human prostate cancer lines. The influence of Ang III and Ang II on classic receptors may be inhibited by Losartan or PD123319. Test peptide modulation of the AT1 and AT2 receptors was examined by Western Blot and fluorescent immunocytochemistry. The results indicate that Ang III promotes the migration of both LNCaP and DU-145 lines, whereas Ang II stimulates this process only in androgen-independent cells. Both angiotensin peptides can induce prostate cancer cell proliferation in a time- and dose-dependent manner. The obtained results show that Ang III and Ang II can modify the expression of classic receptors, particularly AT2. These results suggest that the investigated peptide can modulate cell migration and proliferation in prostate cancer cells. Angiotensins probably have a greater influence on proliferation in the early-stage prostate cancer model than hormone-independent cell lines. Assume also that Ang II can enhance the migration tendency aggressive prostate cancer cells, while Ang III does so more effective in non-metastatic cells.

1. Introduction

Statistics show that, in 2011, about 240,890 men received a prostate cancer diagnosis and an estimated 32,720 men died from the disease [29]. Due to the asymptomatic nature of this tumor, a large proportion of prostate cancer cases are detected at the stage of metastasis. Prostate cancer kills patients essentially because of the migratory nature of their cells. Cellular migration is critical to cell scattering, tissue invasion and metastasis. The migration potential of prostate cancer cells is dependent on complex molecular mechanisms [2,9,27].

The renin–angiotensin system (RAS) has been described as a regulator of many physiological and pathological processes in several kinds of reproductive tissue, including that of the breast [6,13,17,37], uterus [11,23], ovarian [6,12,13,17], testis [25] and prostate [5–7,13,17,19,20,33,34]. The main elements of RAS, such as angiotensinogen, angiotensin peptides (e.g. Ang II, Ang III, Ang IV), angiotensin-converting-enzymes (ACE-1, ACE-2) or angiotensin receptors (AT1, AT2, AT4) are expressed in the human prostate. Changes to this system have been noted in benign prostatic hyperplasia (BPH) and prostate cancer (PC). Ang II is an important bioactive peptide of RAS, which is converted into angiotensin III by aminopeptidase A. This heptapeptide (Ang III) can in turn be converted to shorter fragments by several peptidases. Ang III has physiopharmacological activities similar to those observed for Ang II. Both peptides can mediate signal transduction via interaction with at least two specific membrane receptor subtypes: AT1 and AT2. Results from numerous studies indicate that angiotensin peptides like Ang II, and shorter ones like Ang III, may have an important role in promoting processes related to prostate tumorigenesis and metastasis, including cell proliferation, adhesion and migration [5,19,20,33].

The aims of this study were to compare the effects of two peptides from the angiotensin family (Ang III, Ang II) on cell migration and cell division in androgen-dependent (LNCaP) and

Abbreviations: Ang II, angiotensin II; Ang III, angiotensin III; RAS, renin–angiotensin system; AT1, angiotensin receptor type 1; AT2, angiotensin receptor type 1; ACE, angiotensin-converting-enzymes; BPH, benign prostatic hyperplasia; PC, prostate cancer; PD123319, AT2 inhibitor; FBS, fetal bovine serum; MAPK, mitogen-activated protein kinase.

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androgen-independent (DU-145) prostate cancer cell lines. In addition, since Ang III binds with a lower affinity to AT1 and AT2 receptors than Ang II, the second aim was to evaluate the influence of Losartan (AT1 inhibitor) and PD123319 (AT2 inhibitor) on the biological effects of angiotensin peptides. The potential relationship between Ang III and Ang II regarding the expression of the classic angiotensin receptors was also assessed.

2. Materials and methods

2.1. Cell lines

Cell lines were obtained from the ATCC (American Type Culture Collection). The weakly-tumorigenic and nonmetastatic prostate cancer cell line, LNCaP, established from a lymph node metastasis, was used as a model of early stage androgen-dependent prostate cancer. The aggressive and tumorigenic DU-145 cell line, derived from brain metastases, was used as a model of late stage androgen-independent disease [19]. Both prostate cancer cell lines were incubated at 37 °C in a humidified atmosphere of 5% CO_2 in air. LNCaP was cultured in RPMI 1640 medium and DU-145 was cultured in DMEM supplemented with 10% heat-inactivated FBS (fetal bovine serum), 2 mM L-glutamine, 1 mM sodium pyruvate and antibiotics (penicillin 50 U/ml; streptomycin 50 μg/ml; neomycin 100 μg/ml) (Life Technologies/Gibco). The medium was changed every 48 h. Cells were harvested with 0.25% trypsin/EDTA.

2.2. Reagents

Angiotensins II and III were purchased from Bachem. The selective AT1 receptor antagonist (Losartan) was kindly provided by Prof. Pawlikowski (Medical University of Lodz). PD123319, a potent and selective non-peptide AT2 angiotensin II receptor antagonist, was obtained from Sigma.

2.3. Cell migration assays

2.3.1. Wound healing test

The androgen-independent prostate cancer cell line was seeded in 12-well plates and incubated overnight in standard growth medium at 37 °C and 5% CO_2. A uniform scratch was made in 100% confluent monolayer culture. The wound was introduced by scraping the monolayer with a sterile 200 μl pipette tip and washing it with sterile PBS to remove cell debris. Angiotensins III or II (5 nM) were added, and wound closure was documented by photography of the same region at different times (0–48 h). Using the ImageJ software, the area of each wound was calculated at each time point (0 h, 24 h and 48 h). Data are expressed as percentage wound closure compared to the original free space (0 h = 100% of the total area). The results were presented as means three independent experiment.

2.3.2. Transwell migration chamber

LNCaP and DU-145 cells were added to inserts (BD Falcon) contain a 3 μm pore size polyethylene terephthalate membrane at a final concentration of 10^6 cells/ml in 300 μl of serum-free medium with or without angiotensin (5 nM). The lower chamber contained 900 μl of medium with 10% fetal bovine serum. After 48-h incubation at 5% CO_2, 37 °C, the non-migrating prostate cells from the interior of the inserts were mechanically removed. Cells that migrated to the lower surface of the membrane were stained with staining solution (10 mg crystal violet, 5 ml ethanol 95% and 45 ml distilled water) for 20 min. The stained cells were dissolved in 10% acetic acid and the absorbance was read on a spectrophotometer at 560 nm (BioTek). The values are expressed as percentage relative to the untreated control. Each point is the average ± SEM of three individual experiments.

2.4. Cell proliferation assays

2.4.1. Countess automated cell counter

The cells were seeded in a 12-well flat-bottom plate with angiotensin (5 nM Ang III; 5 nM Ang II) or a combination of angiotensin and Losartan (5000 nM). The control cells were grown under the basic medium without angiotensin or Losartan. The cells were collected 24 h later by trypsinization and were evaluated with a 0.1% trypan blue exclusion test using a Countess Automated Cell Counter (Life Technologies™). A single sample measurement using this counter provided the following data: total cell concentration, viable and dead cell concentration and cell size.

2.4.2. Cell prolifertation ELISA, BrdU (colorimetric)

The BrdU Immunohistochemistry Assay Kit was produced by Roche. This non-isotopic immunoassay analyzes the proliferation of cells by incorporating bromodeoxyuridine (BrdU), an analog of the DNA nucleotide thymidine, into the synthesized DNA of actively dividing cells. The extent of BrdU incorporation is reflected in the intensity of absorbance of the final reaction.

The cells were seeded in a 96-well flat-bottom plate (2×10^4 cells/well) and were maintained overnight in complete medium in 5% CO_2, 37 °C. The cells were then incubated (24 h) in Ang III or Ang II (0.05–5 nM) with or without inhibitors (5000 nM Losartan or PD123319). The control cells were grown under the same conditions, in the same medium but without the compounds mentioned above. BrdU was added to the culture medium in the last hour of incubation, according to the manufacturer's instructions (Roche). The colored reaction product was quantified using a micro plate reader (BioTek) at a wavelength of 450 nm. Each point is the average ± SEM of three individual experiments, each performed in triplicate. The percentage of proliferating cells was calculated relative to the untreated control.

2.5. Protein detection assays

2.5.1. Fluorescent immunocytochemistry

Both prostate cancer cell were seeded in a 6-well flat bottom plate and incubated overnight. After 24 h, the cells were fixed in cold fixing solution (95% ethanol, 5% acetic acid) for 20 min. After a 60-min incubation at 37 °C with rabbit polyclonal antibodies for AT1 and AT2 (Santa Cruz Biotechnology; sc-1173, sc-9040), the wells were washed with PBS. The cells were then incubated with secondary antibody coupled to Alexa Fluor (red) (Life Technologies™) for 60 min in a dark place at room temperature. The nuclei were visualized with DAPI staining (blue) (Sigma). The images were observed and photographed with the FLoid Cell Imaging Station (Life Technologies™) which offers simple fluorescent cell imaging.

2.5.2. Western blot

The prostate cancer cells (passage number between 5 and 20) were incubated for 24 h in the presence or absence of 5 nM angiotensins. The detailed procedures for protein isolation and Western blot analysis have been previously described [8]. Primary antibodies (Santa Cruz Biotechnology; anti-AT1, anti-AT2 and loading control anti-GAPDH) were detected using conjugated peroxidase-labeled secondary antibodies (Sigma). Bands were visualized using Sigma-Fast BCIP/NBT reagent (Sigma). Quantitative analysis of protein levels was measured densitometrically using Quantity One Bio-Rad software. To avoid sample loading errors, GAPDH expression was determined in the blots to adjust and normalize the amount of sample loaded. The densitometry values were

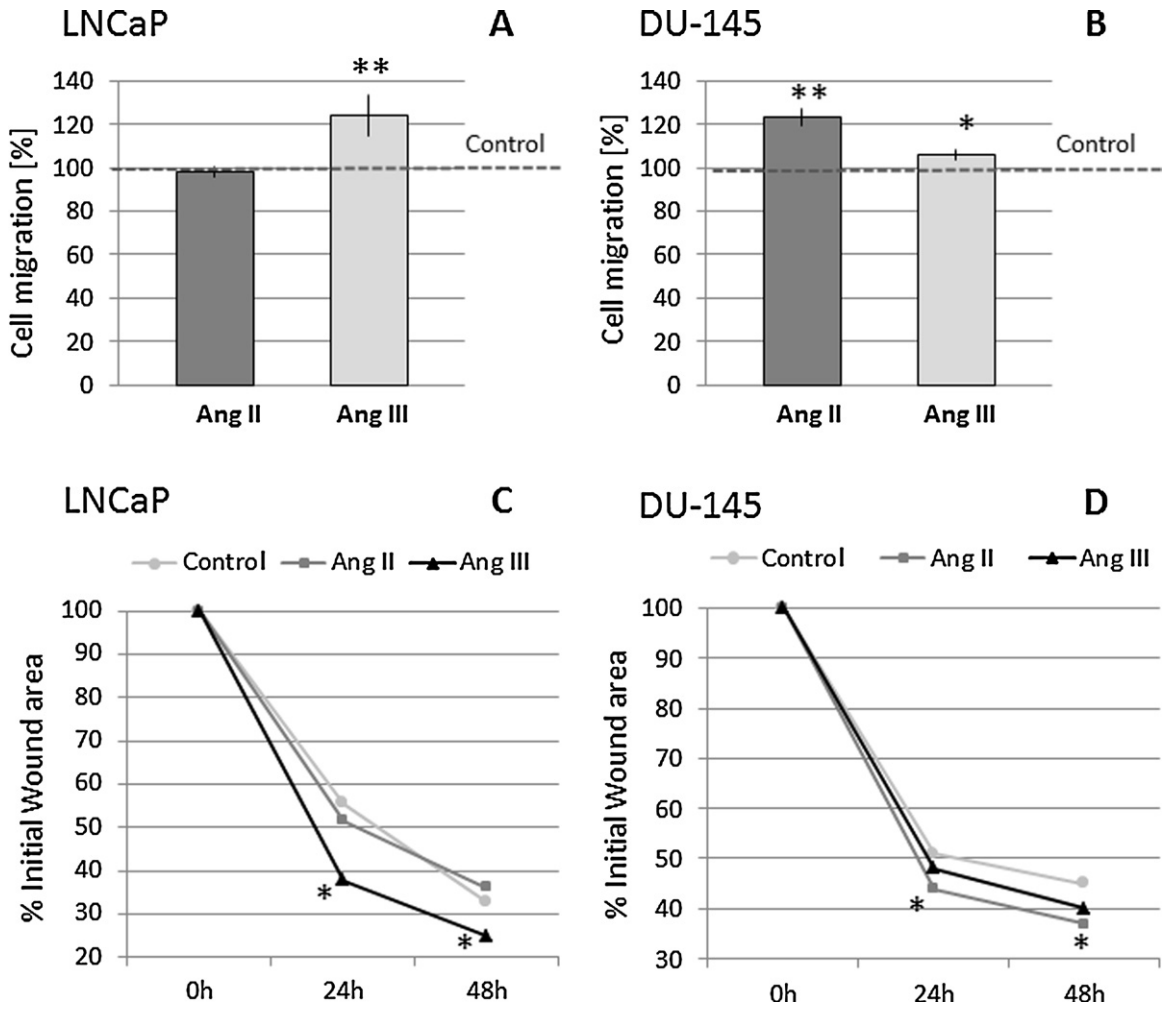

Fig. 1. Effects of Ang II and Ang III (5 nM) on cell migration of prostate cancer cell lines: LNCaP (A and C) and DU-145 (B and D) after 24 and 48 h incubation. Upper panels present the results in Transwell Migration Chamber Assay (A and B). Line graphs (C and D) show the results of the Wound Healing Assay. Asterisk indicates significant differences (*$p < 0.05$) compared to controls.

calculated as the mean relative density (in arbitrary units) of bands compared with control samples.

3. Statistical evaluation

All results presented in this study are expressed as mean values ± SEM. Statistical significance was evaluated using analysis of variance (One-Way ANOVA) for repeated measurements followed by LSD post hoc tests to determine the extent of the differences using the StatGraphics Plus 6.0. The accepted level of significance was $p < 0.05$. The results are presented as mean ± SEM.

4. Results

4.1. Effect of Ang III and Ang II on cell migration

To assess the effect of Ang III and Ang II activation on prostate cancer cell migration in vitro, inserts containing a 3 μm pore size PET membrane were used, as well as wound-healing assays. The results indicated that Ang II stimulated the migration of androgen-independent prostate cancer cells (Fig. 1B) but not androgen-dependent cells (Fig. 1A), whereas Ang III had the opposite effect; it promoted cell migration of LNCaP to a much greater degree than DU-145. Fig. 1D showed the acceleration of wound closure cells treated with Ang II (5 nM) as compared with those in untreated control groups of DU-145 prostate cancer cells. Wound-healing data revealed (Fig. 1C) that wound repair in LNCaP cells after Ang II treatment was delayed compared with LNCaP cells after Ang III incubation.

4.2. Effect of Ang III and Ang II on cell proliferation

The influence of Ang III and Ang II on cell proliferation was determined by BrdU assay and a countess automated cell counter. As can be seen in Fig. 2A and B, Ang II significantly stimulated cell proliferation in the androgen-dependent prostate cancer cell line at all concentrations and incubation times. The effects of Ang III after 24 h of incubation were similar those seen in the control, except for the highest concentrations. Ang III at a concentration of 5 nM induced a weak increase in the proliferation of LNCaP cells. Prolonged exposure to the peptide (48 h) strongly increased bromodeoxyuridine incorporation into DNA in the synthetic (S) phase of the cell cycle (Fig. 2B). Furthermore, the observed effect was much stronger than that of Ang II.

Fig. 2C shows that Ang II slightly but significantly inhibited cell proliferation in the androgen-independent prostate cancer cell line at all concentrations after 24 h of incubation. However, this effect was reversed by a prolonged incubation period of 48 h. In DU-145 cells, Ang III weakly intensified BrdU incorporation, but only at concentrations of 0.5 and 5 nM and where the incubation time was

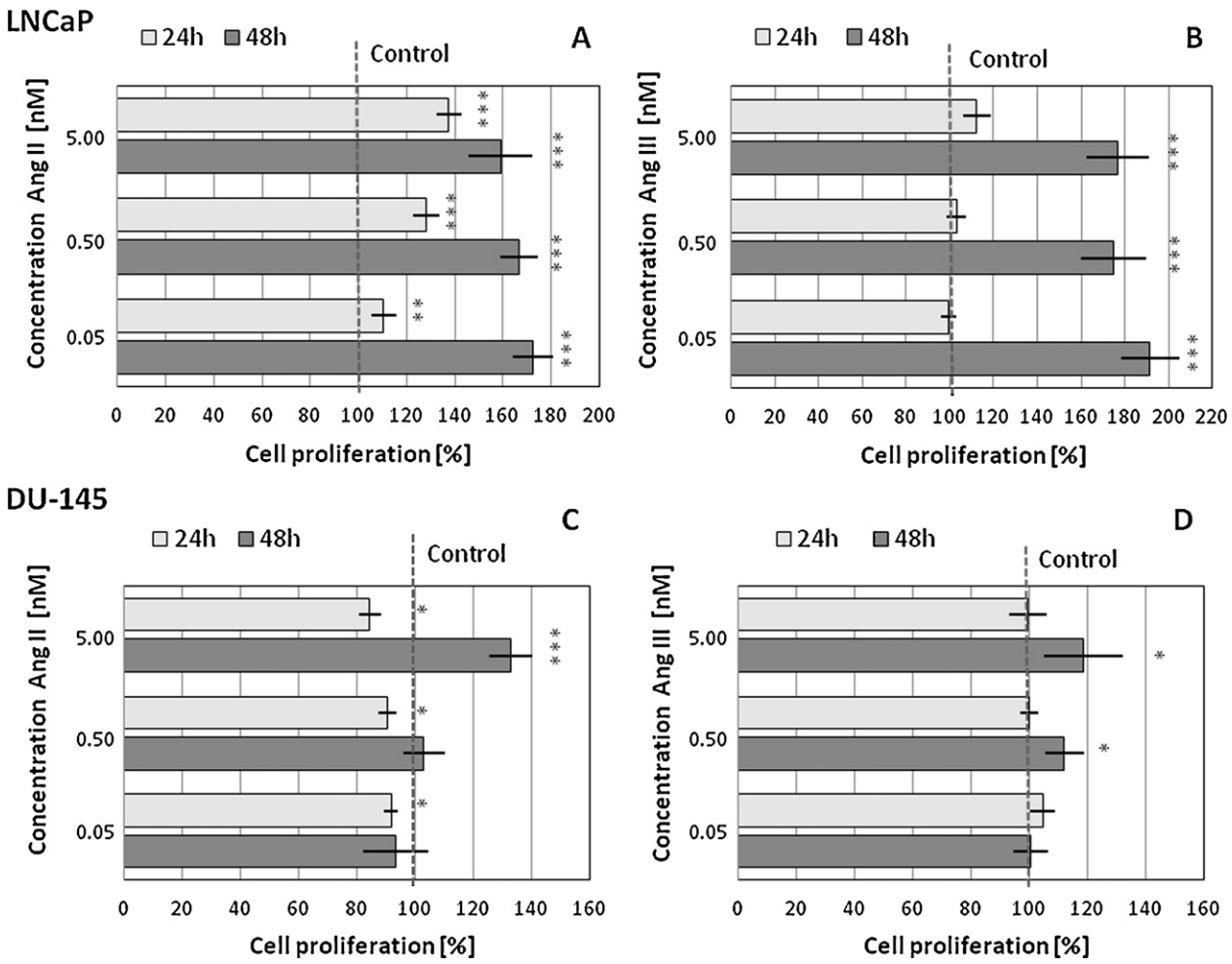

Fig. 2. Effects of Ang II and Ang III on the cell proliferation of prostate cancer cell lines: LNCaP (Ang II – A; Ang III – B) and DU-145 (Ang II – C; Ang III – D) at different incubation times (24 h, 48 h). The asterisk shows significant differences ($^{*}p < 0.05$; $^{**}p < 0.01$ $^{***}p < 0.001$) (mean ± SEM) compared to controls.

extended to 48 h (Fig. 2D). In this case, Ang II (5 nM) induced a stronger stimulatory effect on cell proliferation than Ang III (5 nM).

4.3. Effect of angiotensin receptor antagonists on prostate cancer cells

The influence of AT1 and AT2 angiotensin receptor blockers was investigated with Losartan and PD123319, respectively. As can be seen in Fig. 3A, both receptor blockers significantly negated the inhibitory effect of Ang II in androgen-dependent prostate cancer cells, although the effect of Losartan (Fig. 3A and C) was much stronger than that of PD123319 (Fig. 3A). There were no differences in the exposure of androgen-independent prostate cancer cells to Ang II or Ang III and combination of these peptides with inhibitors (Fig. 3B and D).

4.4. Effect of Ang III and Ang II on the levels of classic angiotensin receptors

Immunohistochemistry and Western blot analysis showed that both of the classic angiotensin receptors AT1 and AT2 are present in LNCaP and DU-145 cells (Fig. 4). Western blots were performed to investigate the protein level changes of AT1 and AT2 receptors in prostate cancer cell lines (Fig. 4) treated with Ang III or Ang II (5 nM). The results confirm our previous findings that these two classic angiotensin receptors are present in LNCaP and DU-145 cells [20]. In addition, peptides Ang III and Ang II were found to induce a significant decrease of angiotensin receptor subtype 2 in both cell lines (Fig. 4C and D). Furthermore, reduced AT1 receptor content could be observed in the androgen-dependent prostate cancer line after a 24 h-incubation with Ang II (Fig. 4A).

5. Discussion

The anatomical and physiological characteristics of the prostate predispose it to disease processes such as inflammation, proliferative dysplasia and hyperplastic and neoplastic changes. Prostate cancer is the most common malignancy of the male genitourinary tract. The majority of prostate tumors are androgen dependent, meaning that they respond to androgen-ablation therapy. However, these tumors will eventually become refractory to androgens [9,27].

The two prostate cancer cell lines used in the study were characterized by a different invasive potential in vitro, as well as different sensitivity to androgen [30]. These results confirm our previous observations [8,22] that the biological properties of angiotensins are associated with the hormonal status and invasive potential of prostate cancer cells.

Cell migration is a process which is essential during cell invasion and metastasis. Prostate cancer typically causes no symptoms in its early stages for that reason; this type of cancer is often fatal, essentially because of the migratory nature of its cells [2,27]. Several reports have demonstrated that angiotensin II can regulate adhesion, invasion and cellular migration in certain reproductive

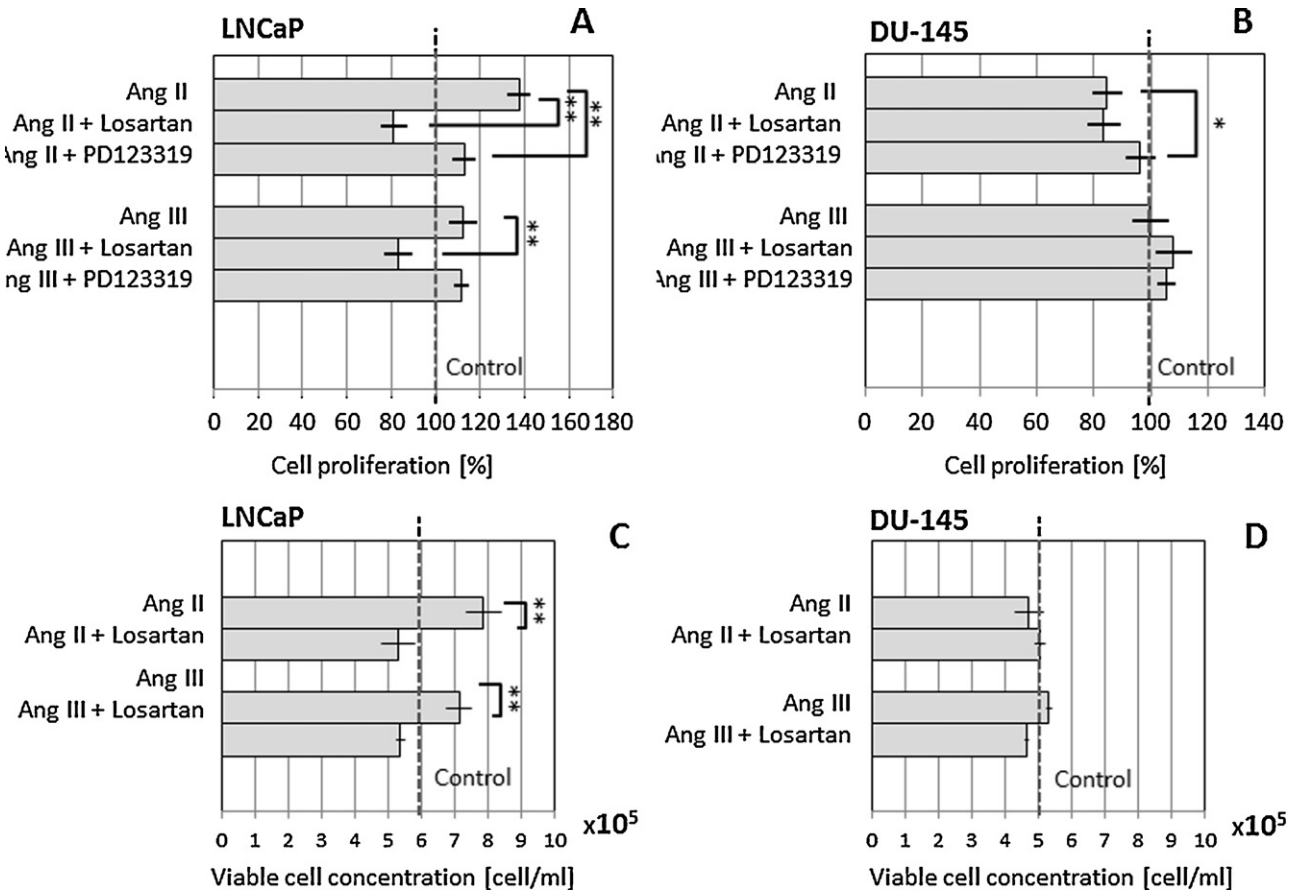

Fig. 3. The influence of inhibitors AT1 (5000 nM Losartan) and AT2 (5000 nM PD123319) on angiotensin-induced (5 nM Ang II or 5 nM Ang III) effects on prostate cancer cell lines after 24 h incubation. Upper panels present the colorimetric analysis of BrdU incorporation into prostate cancer cells: LNCaP (A) and DU-145 (B). Histograms C and D show the changes in the number of prostate cancer cells: LNCaP and DU-145, respectively (countess automated cell counter). Asterisk indicates significant differences ($^{*}p < 0.05$; $^{**}p < 0.01$) (mean ± SEM) compared to controls.

cancer cell lines [12,24,25,34]. Therefore, it was decided to investigate how angiotensin III and III treatment would influence hormone-dependent and hormone-independent prostate cancer cell migration.

Interestingly, Ang III increases cell migration in both cell lines, while Ang II acts as a stimulant only for DU-145 cells. Additionally, it is worth noting that Ang III promoted the migration of LNCaP cells more intensely than DU-145 cells. The results may suggest that while Ang II enhances the migration character of aggressive cancer cells, Ang III is responsible rather for stimulating the migration potential of nonmetastatic cells. A study by Puddefoot et al. [24] reported that Ang II inhibits adhesion and migration of poorly invasive/nonmetastatic breast cancer cells from the MCF-7 line. On the other hand, Suganuma et al. [31] note that Ang II increases the invasive potential of the highly-metastatic ovarian cancer cell line SKOV3. In both literature cases, the angiotensin subtype 1 receptor was responsible for migration activity [35,36]. However, further studies are required to assess of the tendency.

Cell survival and proliferation plays an important role in growth and cancer development. Using a BrdU incorporation assay as an indicator of cell proliferation, it was noted that Ang II stimulates DNA synthesis in LNCaP cells but not in DU-145 cells. In addition, it was observed that Ang II significantly inhibits the cell growth of the DU-145, the hormone-independent line, after 24-h incubation. This observation was unexpected because earlier results have shown that Ang II stimulates cell proliferation in normal and prostate cancer cell cultures [35,36]. However, Chow et al. demonstrated that Ang II did not stimulate DNA synthesis in another hormone-independent prostate cancer cell line (PC3) [4]. A study by Ławnicka et al. reported that Ang II could decrease the growth of DU-145 cells in vitro [16]. However, no growth-inhibitory effects of shorter angiotensin fragment were observed in these cells in this study. In fact our results clearly demonstrate that Ang III can enhance the cell proliferation potential of DU-145 cells after a 48-h application. There is also the possibility of partial conversion of Ang II to Ang 1–7. Meanwhile some scientists suggest that Ang 1–7 may serve as an anti-proliferation, anti-angiogenic and anti-metastatic agent for cancer [10,14,15].

As shown in the present study, both AT1 and AT2 are present in LNCaP and DU-145 cells. Uemura et al. [36] found that AT1 receptor mRNA was strongly expressed in LNCaP cells and was moderately expressed in DU-145 cells. The present study confirms our earlier observations regarding the amount of protein [8]. Although AT2 receptor mRNA has been identified in LNCaP by many researchers [4,8,18,21], there is much less information about its expression in DU-145 cells [3,28]. In general, the AT1 receptor mediates growth-promoting effects, whereas the anti-proliferative effects are mediated by AT2. However, there are some indications that both receptors can generate signals for both proliferation and apoptosis [25].

In our earlier studies we noted that angiotensin receptor blockers (Losartan and PD123319) when added alone to the culture medium at concentration 5000 nM, diminished cell proliferation in androgen-dependent line but not androgen-independent cells.

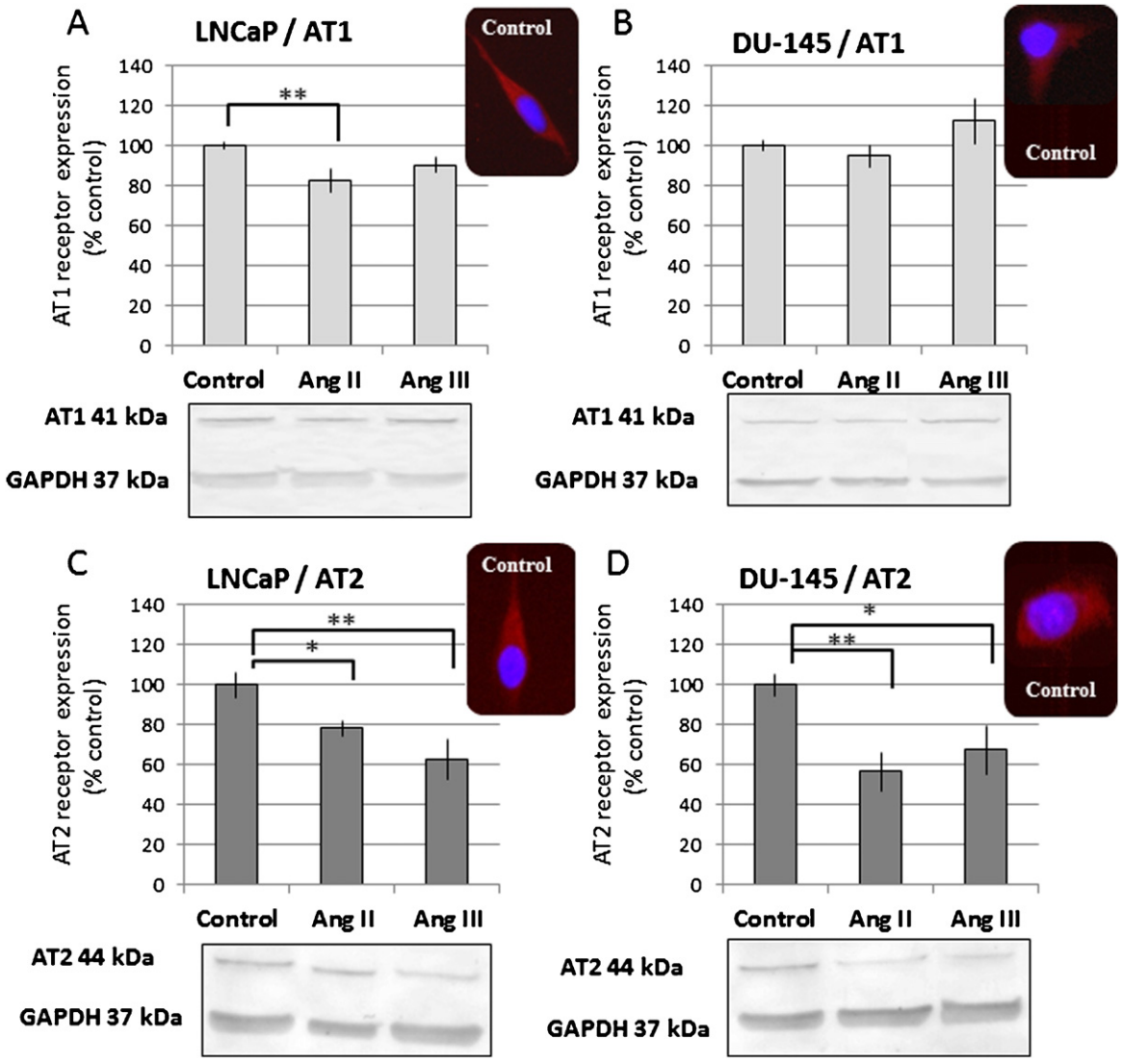

Fig. 4. Effects of Ang II and Ang III (5 nM) on the level of classic angiotensin receptors in prostate cancer cell lines: LNCaP (A and C) and DU-145 (B and D). The upper panel shows statistical analysis and a representative Western Blot for AT1. The lower panel shows statistical analysis and a representative Western Blot for AT2. Furthermore, each panel shows the image immunocytochemistry of angiotenisn receptors in prostate cancer cells. Asterisk indicates significant differences ($^{*}p < 0.05$; $^{**}p < 0.01$) (mean ± SEM) compared to controls.

The detailed results were as follows: in LNCaP cells, blocker-AT1 and blocker-AT2 decreased cell proliferation to 87% ± 3 and 84% ± 2 of the control value, respectively [8].

Much of the research in this area notes that Ang II motivates cell growth in the LNCaP cell line in a time- and/or dose-dependent manner [6]. Our present study confirms its stimulatory effect of in androgen-dependent prostate cancer cells. Uemura et al. [36] demonstrated that Ang II enhances the proliferation of prostate cancer cell lines via the AT1 receptor. However, Teranishi et al. [32] noted that the autocrine effect of angiotensin on cell proliferation is dependent on the functional state of both AT1 and AT2 receptors. Here, both receptor blockers negated the inhibitory effect of Ang II in LNCaP cells, although Losartan was much effective than PD123319.

Interestingly PD123319 (5000 nM) blocked the inhibitory effect of Ang II in DU-145 cells (Fig. 3). Furthermore, lower distribution volumes of AT2 in DU-145 cells were noted after Ang II treatment. These findings, together with data published previously by us suggested that reducing the level of AT2 receptor in DU-145 may reverse the inhibitory effect of Ang II by prolonging the incubation period (48 h).

It has been observed that that Ang II and Ang III may synergistically stimulate cell growth and angiogenesis [32]. Consequently, both of these peptides can be involved in the development and progression of prostate cancer. The proliferative signal transduction of Ang III, as for Ang-II, also seems to be via MAPK phosphorylation. This study demonstrates that both Ang III and Ang II can activate prostate cancer cell proliferation. The stimulatory effect of Ang III on both prostate cancer cell lines was observed only after prolonged incubation (48 h). In the case of LNCaP cells, this effect was much greater than that of Ang II.

According to Teranishi et al. [32], the proliferative effect of Ang III was inhibited by olmesartan, an AT1 receptor blocker. Similar effects were seen in this study for Losartan. It has been proposed that Ang III has a lower affinity than Ang II to classic angiotensin receptors. On the other hand, Ang III, in various tissues, is more selective at the AT2 than the AT1 receptor [1,26]. In this study, a significantly lower amount of AT2 was observed in both prostate cancer cell lines after Ang III treatment, implying that reducing the level of AT2 receptor in LNCaP and DU-145 cells may be the cause of the stimulatory effect of Ang III, by prolonging the incubation period (48 h).

In summary, the results demonstrate that Ang III and Ang II investigated in the study can modulate cell migration and proliferation in prostate cancer. The results suggest that Ang II can enhance the migratory character of aggressive prostate cancer cells, while Ang III is more responsible for stimulating the migration of non-metastatic cells. Furthermore, angiotensin peptide has a greater potential to induce proliferative activity on hormone-dependent human prostate cancer than on androgen-independent, late stage disease. It seems that the key role in the cell response to angiotensin peptides is played by changes in the expression of AT1 and AT2 receptor.

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