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Coupling of α_1-Adrenoceptors to ERK1/2 in the Human Prostate

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Key Words
Prostate hyperplasia · α_1-Adrenoceptor · Extracellular signal-regulated kinase · Smooth muscle · Lower urinary tract symptoms · α1-Adrenoceptor blocker

Abstract
Introduction: α_1-Adrenoceptors are considered critical for the regulation of prostatic smooth muscle tone. However, previous studies suggested further α_1-adrenoceptor functions besides contraction. Here, we investigated whether α_1-adrenoceptors in the human prostate may activate extracellular signal-regulated kinases (ERK1/2). ***Methods:*** Prostate tissues from patients undergoing radical prostatectomy were stimulated in vitro. Activation of ERK1/2 was assessed by Western blot analysis. Expression of ERK1/2 was studied by immunohistochemistry. The effect of ERK1/2 inhibition by U0126 on phenylephrine-induced contraction was studied in organ-bath experiments. ***Results:*** Stimulation of human prostate tissue with noradrenaline (30 μM) or phenylephrine (10 μM) resulted in ERK activation. This was reflected by increased levels of phosphorylated ERK1/2. Expression of ERK1/2 in the prostate was observed in smooth muscle cells. Incubation of prostate tissue with U0126 (30 μM) resulted in ERK1/2 inhibition. Dose-dependent phenylephrine-induced contraction of prostate tissue was not modulated by U0126. ***Conclusions:*** α_1-Adrenoceptors in the human prostate are coupled to ERK1/2. This may partially explain previous observations suggesting a role of α_1-adrenoceptors in the regulation of prostate growth.

Introduction

It is generally accepted that prostate size (static component) and tone (dynamic component) contribute to lower urinary tract symptoms in benign prostate hyperplasia (BPH) [1]. Prostate smooth muscle tone is critically regulated by α_1-adrenoceptor-mediated contraction [1, 2]. As treatment with α_1-adrenoceptor antagonists is a well-established therapy of lower urinary tract symptoms in patients with BPH [1, 2], understanding α_1-adrenoceptor function in the prostate is of particular interest.

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α_1-Adrenoceptor-induced smooth muscle contraction is mediated by the activation of two intracellular signaling pathways, i.e. the Ca^{2+}-dependent and the Rho kinase-dependent signaling cascades [3]. Studies using extraprostatic cell lines demonstrated that α_1-adrenoceptors may additionally couple to nonmotoric signaling pathways, which are involved in growth, proliferation and differentiation [4, 5]. In vivo studies in rodents and investigations using isolated cultured cells have provided evidence that prostate α_1-adrenoceptors may show such nonmotoric coupling in addition to their role in contraction [6–9]. However, any relevance in intact human prostate tissue has not been tested to date, and any nonmotoric signaling by α_1-adrenoceptors in the prostate is insufficiently understood.

In mice and rats, sympathetic innervation may be involved in experimentally induced prostate hyperplasia by α_1-adrenoceptor activation [6–8]. In cultured prostate stroma cells, α_1-adrenoceptor stimulation may result in proliferation [9]. Extracellular signal-regulated kinase 1/2 (ERK1/2) represents an important mediator of growth and proliferation [10]. Here, we investigated whether α_1-adrenoceptor stimulation in human prostate tissue leads to activation of ERK1/2, and the possible involvement of ERK1/2 in α_1-adrenergic contraction.

Materials and Methods

Human Prostate Tissue

Human prostate tissue was obtained from patients (n = 31) undergoing radical prostatectomy for prostate cancer. Representative tissue sections did not exhibit histological signs of neoplasia, cancer or inflammation. All procedures were approved by the ethics committee of the Ludwig Maximilian University in Munich, Germany, and in accordance with the Helsinki Declaration of 1975, as revised in 1983.

Sampling and in vitro Stimulation

For analysis by immunohistochemistry, samples of prostate tissue were shock frozen in liquid nitrogen after prostatectomy and pathological examination without any additional delay. For in vitro stimulation, prostate tissue specimens were prepared as small strips (2–3 × 1 mm) and allocated to 4 polyethylene tubes containing 10 ml Krebs-Henseleit solution. During the experiments, the tubes were kept at 37°C and continuously oxygenized with carbogen (95% O_2, 5% CO_2). Tissues were allowed to equilibrate for 20 min. For stimulation with noradrenaline or phenylephrine, a 10 mM stock solution was added in the required intervals to obtain the final concentrations of 30 μM or 10 μM, respectively. All samples were exposed to identical experimental conditions and periods, so that the unstimulated samples ('0 min') were incubated as long as all other samples. At the end of each experiment, all samples were shock frozen in liquid nitrogen and stored at –80°C until Western blot analysis was performed. For incubation with U0126, 30 μl of a 10 mM stock solution or solvent (DMSO) was added to obtain a final concentration of 30 μM. Samples were shock frozen after 30 min and stored at –80 °C until Western blot analysis was performed.

Assessment of ERK Activity

ERK1/2 is activated by phosphorylation at threonine 204/tyrosine 202 through mitogen-activated protein kinase (MAPK)/ERK kinase (MEK). For semiquantitative assessment of ERK activity, the ERK phosphorylation state was compared between samples by Western blot analysis with a phospho-specific antibody. After densitometric quantification, phospho-ERK in stimulated samples was expressed as percent of the content in the unstimulated sample.

Western Blot Analysis

Frozen prostate tissue was homogenized in a buffer containing 25 mM Tris/HCl, 10 μM phenylmethanesulfonyl fluoride, 1 mM benzamidine and 10 μg/ml leupeptin hemisulfate, using a FastPrep®-24 system with matrix A (MP Biomedicals, Illkirch, France). After brief centrifugation, supernatants were assayed for protein concentration using the Dc-Assay kit (Biorad, Munich, Germany) and boiled for 10 min with sample buffer (Roth, Karlsruhe, Germany). Samples (20 μg/lane) were subjected to SDS-PAGE, and proteins were blotted on nitrocellulose membranes. The membranes were blocked overnight with blotting-grade milk powder (Roth, Karlsruhe, Germany), and subsequently incubated with primary antibodies. For detection of phospho-ERK and total ERK, the following primary antibodies were diluted 1:500 in phosphate-buffered saline containing 0.1% Tween 20 (PBS-T) and milk powder and applied to membranes: mouse anti-phospho-p44/42 MAPK (ERK1/2) (E10) antibody and mouse anti p44/42 MAPK (ERK1/2) (3A7) antibody (Cell Signaling Technology, Danvers, Mass., USA). Subsequently, membranes were washed with PBS-T, and incubated with secondary peroxidase-coupled antibody (Calbiochem, San Diego, Calif., USA) diluted 1:5,000 in PBS-T containing mild powder. Blots were developed with enhanced chemiluminescence (ECL) using ECL Hyperfilm (GE Healthcare, Freiburg, Germany). Intensities of the resulting bands were quantified using Image J (NIH, Bethesda, Md., USA).

Immunohistochemistry

Sections (6–8 μm) from frozen tissues were stained by an indirect immunoperoxidase technique. Sections were fixed with acetone, and endogenous peroxidase activity was subsequently blocked by 0.03% H_2O_2. Thereafter, sections were blocked with horse serum diluted 1:10 in PBS and incubated with primary mouse anti-p44/42 MAPK (ERK1/2) (3A7) antibody (Cell Signaling Technology). The antibody was diluted 1:50 in PBS at room temperature and incubated with the sections overnight. After washing threefold in PBS, biotinylated secondary horse anti-mouse antibody (Vector Laboratories, Burlingame, Calif., USA) and avidin-biotin-peroxidase complex (Vector Laboratories) were sequentially applied for 30 min each. Staining was performed by using the AEC peroxidase substrate kit (Vector Laboratories) so that brown color represents immunopositive staining. Finally, all sections were counterstained with hemalaun. Control stainings without primary antibodies did not yield any signals.

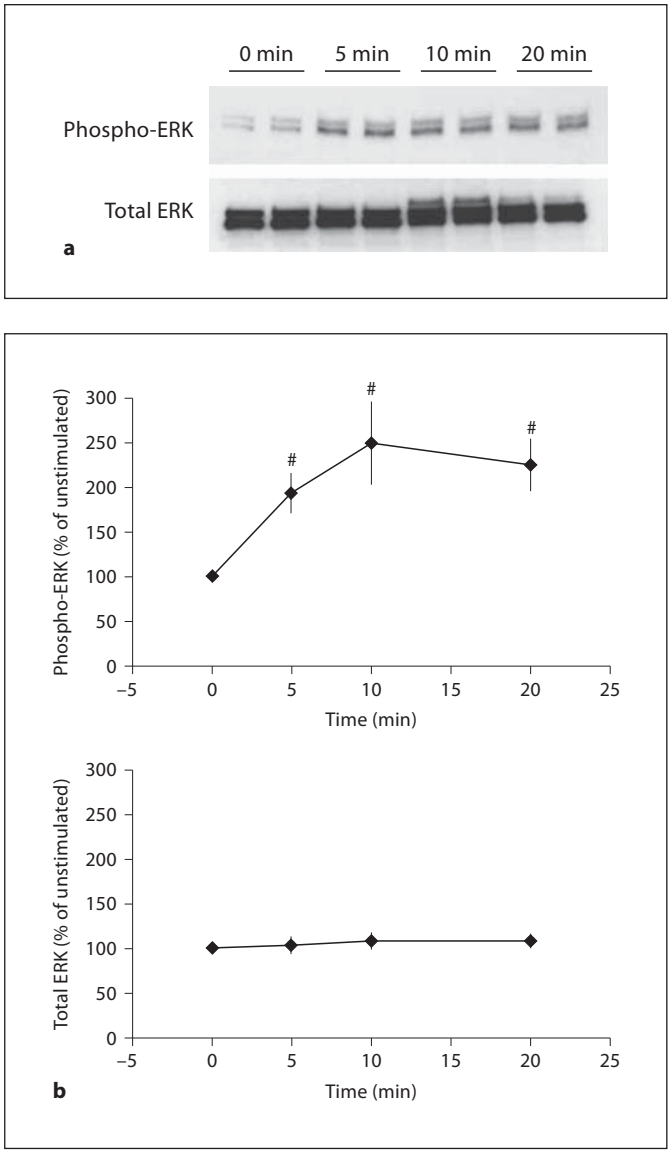

Fig. 1. ERK1/2 activation by noradrenaline in human prostate tissue. Samples of human prostate tissue were stimulated with noradrenaline (30 μM) in vitro. ERK1/2 activity in samples was assessed by Western blot analysis with phospho-specific and non-phospho-specific antibodies, and subsequent densitometric quantification of all experiments. Shown are representative Western blots (**a**) and results from densitometric quantification (**b**); data are means ± SEM from experiments with tissues from 8 patients ($^{\#}p < 0.05$ vs. 0 min). On each Western blot, different stimulated and unstimulated samples are from the same patient.

Measurement of Prostate Smooth Muscle Contraction

Prostate strips (3 × 3 × 6 mm) were mounted in 5 ml aerated (95% O_2 and 5% CO_2) tissue baths (37°C, pH 7.4) containing Krebs-Henseleit solution. Mechanical activity was registered with a Grass Polygraph model 7E (Grass Technologies, West Warwick, R.I., USA). Preparations were stretched to 0.5 g and left to equilibrate for 45 min to attain a stable resting tone. U0126 (30 μM) or solvent (DMSO) were applied 30 min before starting of phenylephrine application. After construction of concentration response curves for phenylephrine, chambers were washed 3 times with Krebs-Henseleit solution, and viability of the preparations was assessed by exposure to a Krebs-Henseleit solution containing 200 mM KCl.

Drugs and Solutions

U0126 is an inhibitor of MEK, which is the specific activator of ERK1/2. U0126 (Cell Signaling Technology) was dissolved in DMSO and kept as 10 mM stock solution at –20°C until use. Aqueous stock solutions of the α_1-adrenoceptor agonist phenylephrine (10 mM; Sigma, St. Louis, Mo., USA) were freshly prepared for each experiment.

Statistical Analysis

Data are presented as means ± SEM with the indicated number of experiments. A two-tailed Student's t test was used for paired or unpaired observations. $p < 0.05$ was considered statistically significant.

Results

ERK1/2 Activation

Significant ERK1/2 activation occurred 5, 10 and 20 min after stimulation with noradrenaline (30 μM), as reflected by increases of ERK1/2 phosphorylation (fig. 1). Thus, 5 min after stimulation with noradrenaline, phospho-ERK1/2 was 194 ± 24% of phospho-ERK1/2 in unstimulated samples ($p < 0.002$). 10 min after stimulation, phospho-ERK1/2 was 250 ± 49% of phospho-ERK1/2 in unstimulated samples ($p < 0.009$). 20 min after stimulation, phospho-ERK1/2 was 226 ± 30% of phospho-ERK1/2 in unstimulated samples ($p < 0.001$). The content of total ERK1/2 did not change during stimulation experiments (fig. 1).

After stimulation with phenylephrine (10 μM), significant ERK1/2 activation occurred after 10 min stimulation, as reflected by an increase in ERK1/2 phosphorylation (fig. 2). Thus, 10 min after stimulation with phenylephrine, phospho-ERK1/2 was 143 ± 16% of phospho-ERK1/2 in unstimulated samples ($p < 0.02$; fig. 2). The content of total ERK1/2 in prostate tissue did not change during stimulation experiments (fig. 2).

Immunohistochemistry

ERK1/2 staining was found in perinuclear regions of prostate smooth muscle cells, and of glandular cells (fig. 3). Control experiments, where the primary antibody was replaced by PBS, did not show any immunoreactivity (fig. 3).

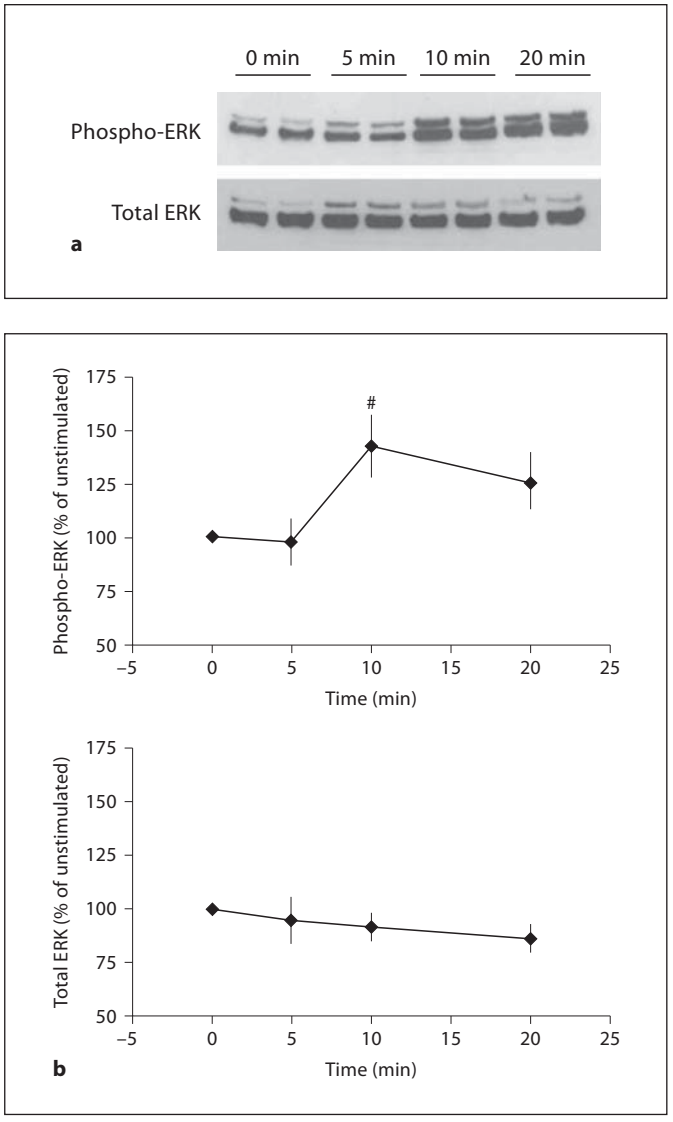

Fig. 2. ERK1/2 activation by phenylephrine in human prostate tissue. Samples of human prostate tissue were stimulated with phenylephrine (10 μM) in vitro. ERK1/2 activity in samples was assessed by Western blot analysis with phospho-specific and non-phospho-specific antibodies, and subsequent densitometric quantification of all experiments. Shown are representative Western blots (**a**) and results from densitometric quantification (**b**); data are means ± SEM from experiments with tissues from 10 patients ($^{\#}p < 0.05$ vs. 0 min). On each Western blot, different stimulated and unstimulated samples are from the same patient.

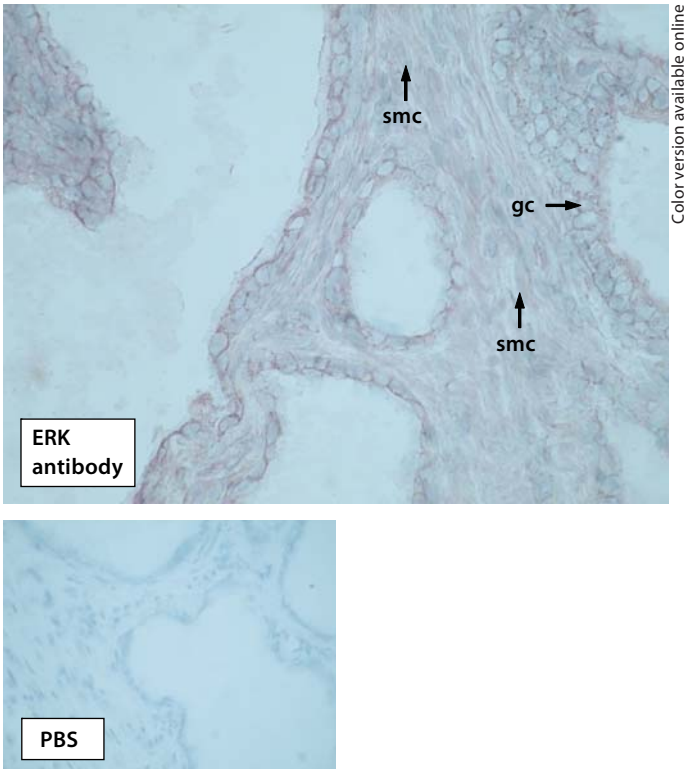

Fig. 3. ERK1/2 expression in human prostate tissue. Sections of human prostate tissue were stained by the peroxidase technique using an ERK1/2-specific antibody (upper panel). In control stainings, the primary antibody was replaced by PBS (lower panel). Shown are representative stainings from experiments with tissues from 5 patients with similar results. Examples for smooth muscle cells (smc) and glandular cells (gc) are indicated by arrows.

Tension Measurements

Phenylephrine induced concentration-dependent contractions of human prostate tissue (fig. 4a). This contraction was not modulated by application of the MEK inhibitor U0126 (30 μM) (fig. 4a). Thus, the maximal phenylephrine-induced contraction was 0.462 ± 0.06 g (30 μM phenylephrine) in prostate strips with DMSO, and 0.498 ± 0.09 g (10 μM phenylephrine) in prostate strips with U0126 (fig. 4a). Likewise, any difference was absent when phenylephrine-induced contraction was expressed as a percentage of high-molar KCl-induced contraction (42 ± 15% of KCl-induced contraction with DMSO, and 37 ± 9% of KCl-induced contraction with U0126, p = 0.783) (fig. 4a).

Effect of U0126 on ERK1/2 Activity

Incubation of intact human prostate tissue with the MEK inhibitor U0126 (30 μM) resulted in a reduced content of phospho-ERK1/2 in these tissues, while the content of total ERK1/2 remained unaltered (fig. 4b). Thus, phospho-ERK1/2 after incubation with U0126 was 17 ± 4% when referred to phospho-ERK1/2 after DMSO incubation (fig. 4b). This reflects inhibition of ERK1/2 by 83 ± 4% in these samples.

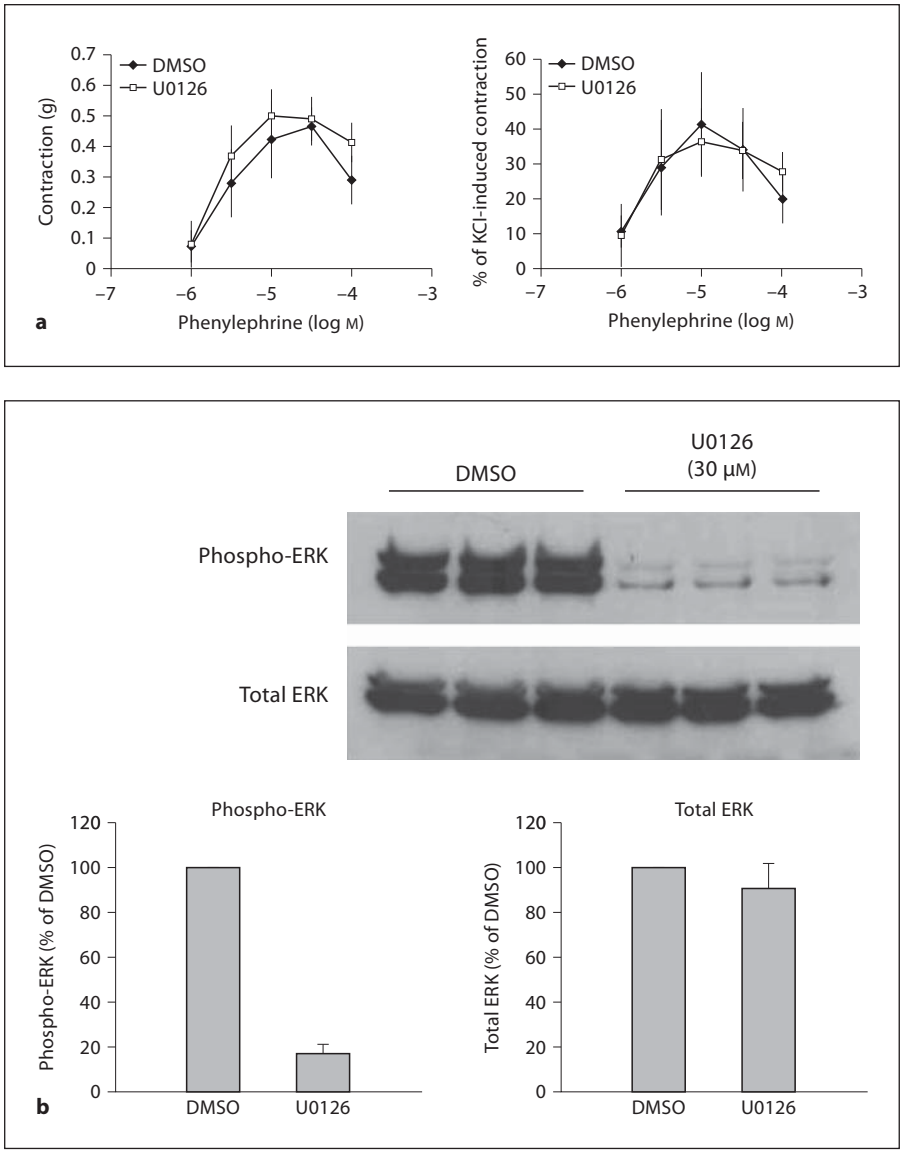

Fig. 4. Effect of the MEK inhibitor U0126 on phenylephrine-induced prostate contraction (**a**) and ERK activity (**b**). **a** Phenylephrine-induced contraction of prostate tissue was determined by myographic measurements. The MEK inhibitor U0126 (30 μM) or solvent (DMSO) was applied 30 min before the first dose of phenylephrine. Concentration response curves for phenylephrine are shown as absolute values in g (left panel), or referred to high-molar KCl-induced contraction (right panel). Data are means ± SEM from experiments with tissues from 5 patients. **b** ERK1/2 inhibition by the MEK inhibitor U0126 is shown. Samples of human prostate tissue were incubated with U0126 (30 μM) or DMSO for 30 min in vitro. Subsequently, ERK1/2 activity in samples was assessed by Western blot analysis with phospho-specific and non-phospho-specific antibodies followed by densitometric quantification of all experiments. Shown are representative Western blots (upper panel) and results from densitometric quantification (lower panels). Data are means ± SEM from experiments with tissues from 3 patients.

Discussion

The current study demonstrates that α_1-adrenoceptors in intact human prostate tissue are coupled to ERK1/2, which is not involved in contractile mechanisms. This may be concluded from three main findings: (1) noradrenaline and phenylephrine stimulation resulted in ERK1/2 activation in intact human prostate tissue, (2) ERK1/2 inhibition did not modulate phenylephrine-induced contraction of human prostate strips, and (3) a major part of ERK1/2 in the human prostate tissue is located to smooth muscle cells.

The contractile function of α_1-adrenoceptors, as well as the expression and distribution of different α_1-adrenoceptor subtypes have been intensively studied in the prostate and lower urinary tract tissues [11]. α_1-Adrenoceptors in prostate smooth muscle cells are coupled to Ca^{2+}/calmodulin-dependent signaling via phospholipase C, and to the RhoA/Rho kinase pathway, which both lead to contraction [3]. Our results suggest that coupling of prostate α_1-adrenoceptors is not confined to these contraction-mediating signaling cascades, but that α_1-adrenoceptors in the human prostate are additionally coupled to the ERK1/2 signaling pathway, which is not involved in α_1-adrenoceptor-mediated prostate smooth muscle con-

traction. ERK1/2 represents a member of the MAPK family and mediates proliferation, growth and differentiation in many different cell types, tissues and species [10].

The activation of ERK1/2 by heptahelical, G protein-coupled receptors has been intensively studied using non-prostatic cell lines [4, 5]. α_1-Adrenoceptor stimulation may lead to ERK1/2 activation in smooth muscle cells, cardiac myocytes and other cell types [4, 5]. We demonstrate that a similar concept is of relevance in human prostate smooth muscle. We assume that ERK1/2 activation observed in our study was at least partially located to smooth muscle cells. As shown by our immunohistochemical stainings, ERK1/2 is expressed in perinuclear regions of smooth muscle and glandular cells in the human prostate. A considerable part of prostate tissue consists of stroma, where smooth muscle cells are a major cell type [1]. This idea of a localization of α_1-adrenergic ERK activation is supported by a previous study, where ERK1/2 expression was observed in isolated cultured human prostatic smooth muscle cells [9]. Interestingly, norepinephrine induced ERK1/2 activation in cultured smooth muscle and stromal cells, but not in cultured epithelial cells in that study [9]. However, neither the type of adrenoceptor mediating this phosphorylation nor any relevance for intact human prostate tissue were identified. In fact, conditions may differ between cultured cells and intact tissues, e.g. due to lacking paracrine regulation of different cell types or due to changed expression patterns during cell culture. Our results show that stimulation of α_1-adrenoceptors does in fact lead to ERK1/2 activation in intact human prostate tissue.

While the role of ERK1/2 for growth of prostate cancer cells is well established [12–15], the function of ERK in prostate smooth muscle cells is less well understood. Indeed, the involvement of ERK1/2 in malignant transformation and proliferation of prostate tumor cells has been studied by numerous authors [16]. As ERK1/2 represents a common regulator of growth and differentiation [10], ERK1/2 likely bears similar functions in prostate smooth muscle cells. Indeed, ERK1/2 mediates proliferation in different lines of cultured prostate stromal cells [13, 17, 18]. Therefore, α_1-adrenoceptor-mediated ERK1/2 activation may be of relevance for the regulation of prostate growth. In rats and mice, (sub)chronic application of phenylephrine in vivo caused hyperplasia and dysplastic changes of the prostate [6, 7]. Another study using sympathectomized rats, suggested a regulation of prostate growth by the sympathetic innervation [8]. In a study using cultured human prostate smooth muscle cells, norepinephrine-induced ERK1/2 activation was associated with proliferation [9]. Together, this led to the assumption that α_1-adrenoceptors may play a role in prostate growth and hyperplasia.

Similar assumptions were additionally raised by observations in studies performed in patients with BPH. Treatment with α_1-adrenoceptor blockers in patients with lower urinary tract symptoms is believed to relieve urine flow at least partially by a decrease in prostate smooth muscle tone [1, 2, 19]. However, it has been proposed that α_1-adrenoceptor blockers may act on BPH by suppression of prostate growth [20–22]. In BPH, the treatment with α_1-adrenoceptor blockers may result in stromal regression and reduced growth [23–27]. On the other hand, regression of prostate volume did not become apparent during the widespread application of α_1-adrenoceptor antagonists in patients with BPH. Treatment with alfuzosin for 3 months did not effectively reduce prostate volume [28]. In another trial, where therapy with terazosin reduced total prostate volume, the authors concluded that further studies are mandatory [28].

The limited effect of α_1-adrenoceptor blockers on prostate size in BPH patients suggest that ERK1/2 activity and growth of the prostate are regulated by numerous different factors in addition to α_1-adrenoceptors. Accordingly, ERK1/2 is well known to be regulated by various nonadrenergic stimuli [10]. Growth factors and cytokines are important regulators of ERK1/2 and growth, which may contribute to prostate hyperplasia together with a α_1-adrenoceptor-dependent regulation [29, 30]. Thus, regulation of prostate growth and ERK1/2 activity in α_1-adrenoceptor blocker-treated patients may be covered by regulation by such growth factors and cytokines.

Conclusions

Our findings demonstrate that α_1-adrenoceptors in intact human prostate tissue are coupled to ERK1/2 in addition to the contraction-mediating pathways. This may explain previous observations suggesting a role of α_1-adrenoceptors in the regulation of prostate growth in patients and rodents, and points to α_1-adrenoceptor functions beyond contraction.

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