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Short communication

The influence of doxazosin, an α_1 -adrenergic receptor antagonist on the urinary bladder contractility in pigs

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Abstract

In the present study influence of doxazosin on the porcine urinary bladder contractility has been examined. Immature pigs were treated for 30 days with: a) doxazosin (n = 5) *per os* at a dose of 0.1 mg/kg b.w. or b) placebo (n = 5; control group). Thereafter, animals were sacrificed and urinary bladder strips from the trigone were suspended in organ baths. The tension of the smooth muscle was measured before and after exposition to acetylcholine (ACh; 10^{-5} – 10^{-3} M), norepinephrine (NE; 10^{-9} – 10^{-7} M) and 5-hydroxytryptamine (5-HT; 10^{-7} – 10^{-5} M). Both the ACh and 5-HT at the highest doses significantly increased the contractility in each group, but this response was weaker in doxazosin-treated animals. NE caused relaxation in both groups, but the effect was weaker in doxazosin-treated group. The results of our study have shown that long-term administration of doxazosin caused a desensitization of the detrusor smooth muscle for *in vitro* applied mediators of the autonomic nervous systems.

Key words: doxazosin, urinary bladder, contractility

Introduction

Alpha1-adrenergic antagonists are the mainstay of pharmacotherapy of primary bladder neck obstruction (Li et al. 2012). All α_1 -adrenergic antagonists (i.e., prazosin, doxazosin, terazosin, tamsulosin, and alfuzosin), although with slight differences in adverse event profiles, are equivalent in effectiveness and efficacy (Cohen and Parsons 2012). Moreover, there are

data supporting the theory that α_1 -adrenergic receptor antagonists are involved in the control of sympathetic and parasympathetic activity to the urinary bladder (Lowe 2004). Although the domestic pig is widely used as an animal model for various human organs, there is still lack of data describing the influence of α_1 -receptors on the urinary bladder. Thus, in the present study we determined the influence of doxazosin, an antagonist of α_1 -adrenergic receptor on the activity of the porcine detrusor muscle.

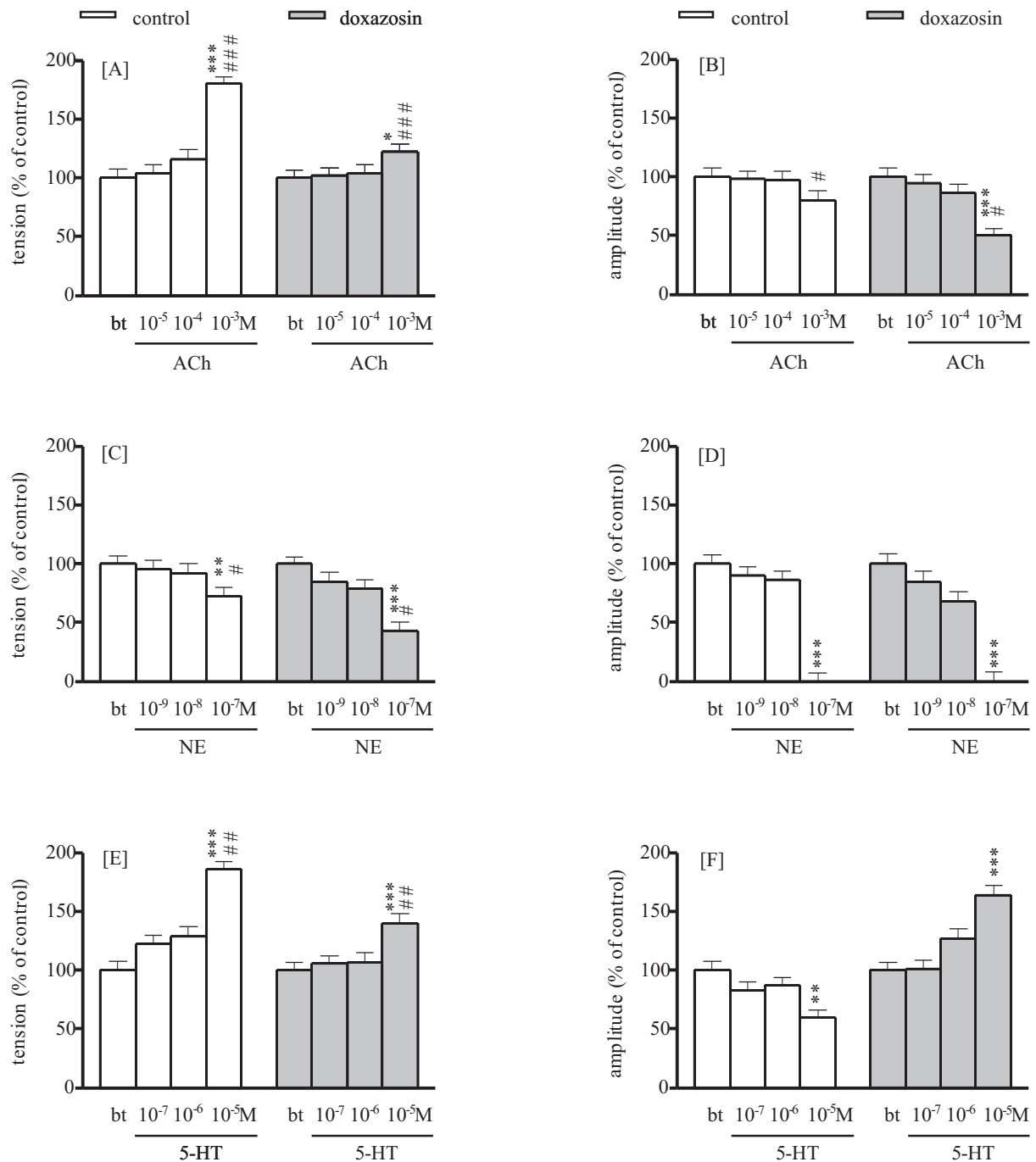


Fig. 1. Influence of acetylcholine (ACh), norepinephrine (NE) and 5-hydroxytryptamine (5-HT) on the tension (A, C, E) and amplitude (B, D, F) of the contraction of the porcine urinary bladder strips of the control and doxazosin-treated group. Bladder wall strips were collected from immature untreated (control group) or doxazosin-treated (30 days, 0.1 mg/kg b.w. *per os*) (doxazosin group). Values (mean \pm SEM; $n = 5$ in each group) are expressed as a percentage of changes in the contractile activity before the treatment. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ as compared to the contractile activity before the treatment. # significant differences between groups after administration the highest dose of substance examined.

Materials and Methods

Immature pigs ($n = 5$; 18 – 20 kg of body weight) were receiving doxazosin *per os* in capsules at a dose 0.1 mg/kg for 30 days; other age-matched pigs ($n = 5$) were used as a control group. After the treatment,

all animals were sacrificed and urinary bladder strips (3x5 mm) from the trigone wall were mounted vertically in 5 ml of organ bath (Schuler Organ bath type 809; Hugo Sachs Electronic, Germany) under conditions of resting tension of 5 mN. The strips were kept in solution of the following composition (mM/l):

NaCl – 120.3, KCl – 5.9, CaCl₂ – 2.5, MgCl₂ – 1.2; NaHCO₃ – 15.5, glucose – 11.5 and pH 7.4, temp. 37°C and continuously saturated with a mixture of 95% O₂ and 5% CO₂. Contractile activity (tension and amplitude) was measured using the Hugo Sachs Electronic force displacement transducer (HSE F30 type 372), and recorded with HSE-ACADW software for Windows 2000 (Germany). After 60 min equilibration, contractile activity was recorded in response to acetylcholine (ACh; 10⁻⁵ – 10⁻³M; Sigma-Aldrich, Germany), norepinephrine (NE; 10⁻⁹ – 10⁻⁷ M; Polfa, Poland) and 5-hydroxytryptamine (5-HT; 10⁻⁷ – 10⁻⁵ M; Sigma-Aldrich). Contractile activity was measured for 10 min before and after administration of each concentration. Between administration of each substance, tissue chambers were washed three times with 15 ml of incubation solution at 10 min intervals. Statistical analysis was performed using Bonferroni multiple comparison test (ANOVA, InStat Graph Pad, San Diego, CA) and p < 0.05 was considered statistically significant. The study procedure was approved by the Local Ethics Committee, University of Warmia and Mazury in Olsztyn, Poland.

Results and Discussion

Changes in the contractile activity of the porcine urinary bladder smooth muscle are shown in Fig. 1. Only the highest doses of examined substances caused significant differences. ACh increased the tension in control (p < 0.001) and doxazosin-treated group (p < 0.05; Fig. 1A), while decreased the amplitude only in doxazosin-treated group (p < 0.01; Fig. 1B) as compared to the period before treatment. Moreover, in doxazosin-treated group, an increase of the tension (p < 0.001) and decrease in the amplitude (p < 0.05) was lower than in the control group. NE decreased the tension in control (p < 0.01) and doxazosin-treated (p < 0.001) group (Fig. 1C) as compared to the period before treatment. The decrease in the tension was higher in doxazosin-receiving group (p < 0.05) as compared to control group. In both control and doxazosin-treated groups, NE decreased (p < 0.001) the amplitude of contractions as compared to period before treatment (Fig. 1D). Administration of 5-HT increased (p < 0.001) the tension in both groups, as compared to the period before treatment (Fig. 1E), however the increase was lower (p < 0.01) in doxazosin-treated group when compared to the con-

trol group. The amplitude of contractions in response to 5-HT was decreased in control group (p < 0.01) and increased in the doxazosin-treated group (p < 0.001; Fig. 1F). The fact that in doxazosin-receiving group the tension of the contractions caused by ACh was lower than in the control group indicates the involvement of the parasympathetic pathway. Our results are similar to these received by Cohen and Drey (1989) and Eroglu et al. (2007) who indicated that α_1 -adrenergic receptor-mediated responses predominated relatively to muscarine responses in bladder neck preparations and are controlled by both α_1 -adrenergic and muscarinic receptors. Moreover, Khan et al. (2000) demonstrated that doxazosin in addition to its α_1 -adrenergic receptor inhibiting activity also inhibits 5-HT-mediated detrusor contractions in rabbit. Obtained results suggest that long term doxazosin administration produce desensitization of detrusor smooth muscle for *in vitro* applied mediators of both sympathetic and parasympathetic nervous systems.

Acknowledgments

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References

- Cohen ML, Drey K (1989) Contractile responses in bladder body, bladder neck and prostate from rat, guinea pig and cat. *J Pharmacol Exp Ther* 248: 1063-1068.
- Cohen SA, Parsons JK (2012) Combination pharmacological therapies for the management of benign prostatic hyperplasia. *Drugs Aging* 29: 275-284.
- Eroglu M, Sezgin A, Semercioz A, Metin A, Kandirali E, Ali Onur M (2007) Contractile responses of rabbit bladder neck to adrenaline, acetylcholine and papaverine after doxazosin treatment. *Int Urol Nephrol* 39: 137-141.
- Khan MA, Thompson CS, Dashwood MR, Mumtaz FH, Mikhailidis DP, Morgan RJ (2000) Doxazosin modifies serotonin-mediated rabbit urinary bladder contraction. Potential clinical relevance. *Urol Res* 28: 116-121.
- Li B, Gao W, Dong C, Han X, Li S, Jia R, Xiao C (2012) Long-term safety, tolerability, and efficacy of α_1 -adrenergic blocker in young men with primary bladder neck obstruction: results from a single centre in China. *Int Urol Nephrol* 44: 711-716.
- Lowe FC (2004) Role of the newer alpha, -adrenergic-receptor antagonists in the treatment of benign prostatic hyperplasia-related lower urinary tract symptoms. *Clin Ther* 26: 1701-1713.