Relaxation Responses of Trigonal Smooth Muscle from Rabbit by Alpha$_1$-Adrenoceptor Antagonists Alfuzosin, Doxazosin and Tamsulosin

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Abstract

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This study was performed to investigate the effects of alfuzosin, doxazosin and tamsulosin *in vitro* on trigone smooth muscle of rabbit. In this study, fifteen rabbits weighing 2.5 - 3 kg were used. One strip in the shape of a trigone was prepared for each of the isolated bladders. Firstly, an initial tension of 1 g was placed on each segment, and we waited for equilibration by constantly bubbling with 95% O_2 and 5% CO_2. Next, the determination level of electrical stimulation which created submaximal contraction and effective dosage were found for trigone and they were determined by applying different concentrations of phenylephrine (10^{-8} M, 10^{-7} M, 10^{-6} M, 10^{-5} M), respectively.

Firstly 10^{-8} M dosage of alfuzosin (10^{-8}M, 10^{-7}M, 10^{-6}M, 10^{-5}M) was added, then we waited for 20 min. Then, an effective dosage of phenylephrine (10^{-5} M) was added into the solution and we waited for 7 min again. After this process, electrical stimulation was applied for the contraction of the tissue. After stimulation, the tissue was washed twice every two minutes and rested; we waited until the tissue reached its starting stretching value. The same processes were performed for the other dosages of alfuzosin (10^{-7}M, 10^{-6}M, 10^{-5}M), doxazosin (10^{-7}M, 10^{-6}M, 10^{-5}M) and tamsulosin (10^{-7}M, 10^{-6}M, 10^{-5}M), respectively.

In conclusion, when we compared the amplitudes of the responses of all concentrations of doxazosin, alfuzosin and tamsulosin in the trigone smooth muscle with amplitude of a response of effective concentration of phenylephrine, it was determined that the prevention level of contractions occurred after tamsulosin hydrochloride was higher than after alfuzosin hydrochloride and doxazosin mesylate. With these results, we showed that alfuzosin, doxazosin and tamsulosin inhibited noradrenalin-based contractions in the rabbit trigone smooth muscle and this result can be used both for *in vitro* and *in vivo* future studies.

Trigone, rabbit, alfuzosin, doxazosin, tamsulosin

Urinary bladder dysfunction secondary to benign prostate hyperplasia (BPH) in humans and animals is a major health problem (Zderic et al. 1996). Nearly 80% of the human male population will seek medical relief for the symptoms which include urgency, frequency, and nocturia (Girman and Guess 2000). It is apparent that these distressing symptoms are the result of significant changes in the physiology and pharmacology of the obstructed bladder (Zderic et al. 1996). The use of alpha (α) blockers to treat BPH is based on their mechanism of action. BPH causes bladder obstruction by two mechanisms: mechanical compression by the adenoma of the urethra and dynamic obstruction of the bladder by prostate smooth muscle compression. Alpha blockers interrupt motor sympathetic adrenergic nerve supply to the prostate which reduces urethral pressure. Three subtypes of α-adrenoceptors, namely, α_{1a} and α_{1b} have been cloned over α_{1d} in recent years (Hieble et al. 1995). The existence

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of different α_1-adrenoceptors in diverse tissues may provide therapeutic opportunity by selectively blocking the desirable subtype in the target tissue without affecting other tissues having other subtypes, thus minimizing the side effects.

Recently, however, attention has been focused on the use of alpha-adrenergic receptor antagonists in patients with this condition. Doxazosin and alfuzosin have been extensively studied and widely used in the treatment of BPH, and tamsulosin is a new drug (Davey 1987; Fulton et al. 1995; Pool 1994; Giuliano et al. 2004). Tamsulosin as a new alpha-adrenergic receptor antagonist has marked antagonistic activity at the numerous alpha-adrenergic receptors present in the smooth muscle within the urinary tract and prostate capsule (O'Leary 2001; Lyseng-Williamson et al. 2002). Thus tamsulosin produces smooth muscle relaxation in these areas and thereby enhances voiding efficiency. In this study, the effects of alfuzosin, doxazosin and tamsulosin of α_1-adrenergic receptor antagonists on the rabbit bladder trigonal smooth muscle will be examined.

Materials and Methods

Preparations of trigonal strips

In this study, New Zealand White male rabbits (2.5 - 3 kg) were anaesthetized by injection of sodium pentobarbital (40 mg·kg^{-1}) into a marginal ear vein and killed by cervical dislocation. Bladder was surgically removed and put into the Tyrode solution (NaCl; 148.9, KCl; 2.7, CaCl; 1.8, $NaPO_4H_2$; 0.2, $NaCO_3$; 11.9, $MgCl_2$; 1.2, glucose; 5.5 mM). Then by extracting the trigone, a piece of stripe tissue in the dimension of 5 - 6 mm × 10 mm was taken. One edge of each trigone tissue preparation was fixed to platinum ring electrodes. The other edge of the tissue was connected to a force transducer and isometric smooth muscle movements were saved via "force transducer" and acquisition system (Biopac MP30 system).

Electrical field stimulation (EFS) and pharmacological responsiveness of trigonal muscles

Trigone samples in organ baths were kept in the Tyrode solution for at least 1 h prior to the recordings to enable the tissues to adapt to the environment, and the solution was refreshed at 15-min intervals. Then optimal tension relationships were achieved with resting tensions of 1g for the trigone strips. Thus, a resting tension of 1 g was applied to the trigone and the sample was left at 38.5 ºC in the Tyrode solution and constantly bubbled with a mixture of 95% O_2 and 5% CO_2. The isometric smooth muscle activity of the trigone samples was monitored and recorded by computer via the force transducer and an acquisition system (MP30 WSW, Biopac Student Lab PRO Software, Biopac Systems). An EFS device (ISO 150-C, MAY, Commat, Ankara,Turkey) was used for electrical stimulation.

After determining the voltage creating submaximal tissue contraction, the dosage response curve of phenylephrine was designated individually for each trigone. Therefore, six different dosages of pheynlephrine were applied (10^{-9} M, 10^{-8} M, 10^{-7} M, 10^{-6} M, 10^{-5} M, 10^{-4} M, respectively,) at submaximal voltage and by giving stimulus to the media after 8 - 10 min, and adding the first 10^{-9} M dosage of phenylephrine. After the application of phenylephrine, by washing the tissue twice every two min, it was allowed to reach its starting stretching value. The other dosages of phenylephrine were put into the media not cumulatively but respectively one by one, and the same process for 10^{-8} M, 10^{-7} M, 10^{-6} M, 10^{-5} M and 10^{-4} M was followed. The phenylephrine-induced maximal contractile responses were calculated as gram for determining the effective dosage.

The effective dosages for each drug were calculated by considering the C_{max} value stated for alfuzosin, doxazosin and tamsulosin. These dosages were calculated as 10^{-8} M, 10^{-7} M, 10^{-6} M and 10^{-5} M for alfuzosin, 10^{-7} M, 10^{-6} M and 10^{-5} M for doxazosin, 10^{-7} M, 10^{-6} M, 10^{-5} M for tamsulosin. Firstly, 10^{-8} M dosage of alfuzosin was added into both goblets and left for 20 min; later an effective dosage of phenylephrine was added and left for 7 min (Szell et al. 2000). The contraction of tissue was induced by giving electrical stimulus. Then, tissues were washed twice for the other dosages of alfuzosin (10^{-7} M, 10^{-6} M, 10^{-5} M). The same processes were followed for dosages of doxazosine (10^{-7} M, 10^{-6} M, 10^{-5} M) and tamsulosin (10^{-7} M, 10^{-6} M, 10^{-5} M). The washing process that was done between the applications was followed respectively in the same manner as stated above.

The contraction values that occur as a result of electrical stimulation in the presence of the effective dosage of phenylephrine were accepted as 100%. By following the same process in the presence of alfuzosin, doxazosin and tamsulosin, the contractions were measured and they were compared with the contractions of the previous application, the prevention ration of drugs' contraction was calculated as percentage.

Statistical analysis

Data were expressed as the mean ± standard deviation (S.D.) with a representing number of specimens. The concentration-response curves to various alpha adrenergic antagonists in trigone smooth muscles were analyzed comparatively using the one-way analysis of variance (ANOVA) test; $p < 0.05$ was considered.

Results

The results of our study are shown in Tables 1 - 2 and Figs 1 - 2. In the study, it was determined that all concentrations (10^{-9} M, 10^{-8} M, 10^{-7} M, 10^{-6} M, 10^{-5} M) of phenylephrine dose-dependently contracted the smooth muscle of the trigone (Table 1). When compared with the responses of phenylephrine and phenylephrine plus alfuzosin, concentrations decreased by 7% in 10^{-8} M concentration, 14% in 10^{-7} M concentration, 20% in 10^{-6} M concentration and 29% in 10^{-5} M concentration, respectively; phenylephrine plus doxazosin concentrations decreased respectively by 22% in 10^{-7} M concentration, 30% in 10^{-6} M concentration and 38% in 10^{-5} M concentration; phenylephrine plus tamsulosin concentrations decreased respectively by 31% in 10^{-7} M concentration, 39% in 10^{-6} M concentration and 48% in 10^{-5} M concentration (Table 2, Figs 1, 2). In the present study, it was concluded that contractions of the rabbit trigone smooth muscle could be prevented by alfuzosin less strongly than by the other two antagonists.

Table 1. The amplitude values (g) in the presence of electrical stimulations (EFS) and the various dosages of phenylephrine (PE) in the rabbit bladder trigone smooth muscle (n = 5).

Concentration (M)	Amplitude (g) mean ± S.D.
EFS	4.86 ± 0.25^{a}
PE 10^{-9} M + EFS	5.09 ± 0.41^{a}
PE 10^{-8} M + EFS	5.33 ± 0.38^{b}
PE 10^{-7} M + EFS	5.55 ± 0.15^{c}
PE 10^{-6} M + EFS	5.72 ± 0.24^{d}
PE 10^{-5} M + EFS	6.22 ± 0.35^{e}
PE 10^{-4} M + EFS	5.62 ± 0.33^{fbcde}

a, b, c, d, e, f: Differences between the values involving different letters on the same column are significant ($p < 0.05$).

Table 2. The amplitude values (g) with the application of electrical stimulus (EFS) of the rabbit bladder trigone smooth muscle in the presence of effective phenylephrine only and various concentrations of alfuzosin hydrochloride (Alf), doxazosin mesylate (Dox) and tamsulosin hydrochloride (Tam) (n = 10).

Treatment	Amplitude (g) mean ± S.D.	Amplitude (%)
PE 10^{-5}M+EFS	6.22 ± 0.85^{b}	100
Alf 10^{-8}M+EFS	5.77 ± 0.79^{ab}	92.76
Alf 10^{-7}M+EFS	5.35 ± 0.76^{ab}	86.01
Alf 10^{-6}M+EFS	4.99 ± 0.77^{ab}	80.23
Alf 10^{-5}M+EFS	4.43 ± 0.70^{ab}	71.22
Dox 10^{-7}M+EFS	4.89 ± 0.79^{ab}	78.62
Dox 10^{-6}M+EFS	4.37 ± 0.80^{ab}	70.26
Dox 10^{-5}M+EFS	3.88 ± 0.79^{ab}	62.38
Tam 10^{-7}M+EFS	4.35 ± 0.82^{ab}	69.94
Tam 10^{-6}M+EFS	3.82 ± 0.82^{ab}	61.41
Tam 10^{-5}M+EFS	3.26 ± 0.80^{a}	52.41

a, b: Differences between the values with different letters in the same column are significant ($p < 0.05$).

Discussion

In this study, comparison of relaxation responses of the rabbit bladder trigone smooth muscle influenced by alpha adrenergic antagonist drugs, alfuzosin hydrochloride, doxazosin mesylate and tamsulosin hydrochloride were researched. $Alpha_1$-adrenergic receptor regulation of prostatic smooth muscle contraction was initially defined by Caine et al. (1975) and Raz et al. (1973) through isometric tension studies of prostate tissue in the presence of noradrenalin. At the end of studies conducted for many years, tamsulosin of alpha adrenergic receptor antagonist with selective pharmacological features that was effective for α_{1a} adrenergic receptors densely present in the prostate tissue was developed (O'Leary 2001). Lyseng-Williamson et al. (2002) stated that the average selectiveness feature for tamsulosin's α_{1a}-adrenergic receptor was 3.9 - 38 times higher when compared with α_{1b}, and 3 - 20 times higher when compared with α_{1d}. Because of tamsulosin's high affinity for receptors, it caused fewer side effects when compared with the other alpha adrenergic antagonists such as doxazosin, terazosin, prazosin and alfuzosin. Doxazosin mesylate and alfuzosin hydrochloride did not show the selective features

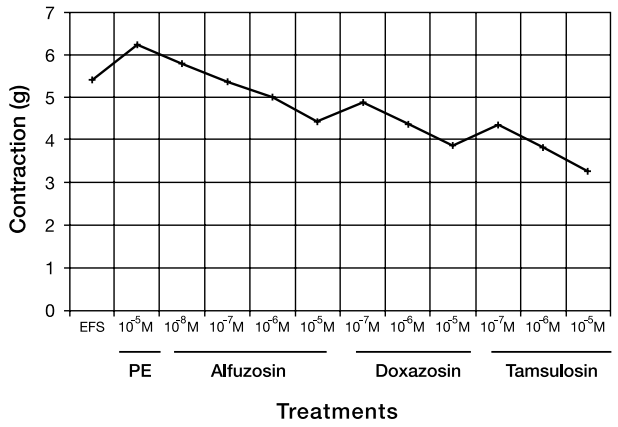

Fig. 1. The amplitude values (g) with the application of electrical stimulus (EFS) of the rabbit bladder trigone smooth muscle in the prsence of effective phenylephrine (PE) only and various concentrations of alfuzosin hydrochloride, daxazosin mesylate and tamsulosin hydrochloride (n = 10).

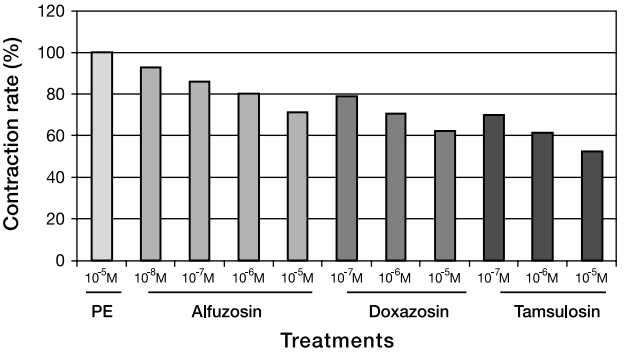

Fig. 2. The amplitude values (%) with the application of electrical stimulus of the rabbit bladder trigone smooth muscle in the prsence of effective phenylephrine (PE) only and various concentrations of alfuzosin hydrochloride, daxazosin mesylate and tamsulosin hydrochloride (n = 10).

for subtypes of adrenergic receptors and they influenced all three receptors in the same ratio (Fulton et al. 1995; Pool 1994).

In the study, it was determined that the contractions caused by EFS in the presence of various concentrations of phenylephrine (10^{-9} M, 10^{-8} M, 10^{-7} M, 10^{-6} M, 10^{-5} M) increased due to the increase of concentration. This fact demonstrated that the contraction created by phenylephrine occurs through adrenergic receptors in the rabbit bladder trigone smooth muscle (alpha-1 and alpha-2). Seo et al. (1999) stated that the effective concentration for phenylephrine was 10^{-5} M in their study. In our study, we found the effective phenylephrine concentration for rabbit as 10^{-5} M, which was similar to findings of Seo et al. (1999) (Table 1). Therefore, the 10^{-5} M dosage of phenylephrine which induced the maximal contraction was chosen as the effective concentration used in the experiment (Table 1 and Fig. 2). However, it was stated in studies conducted on various tissues with phenylephrine that a concentration at which maximal contraction was induced was 10^{-2} M (Van Der Graaf et al. 1996) for the aorta, 10^{-5} M (Karadeniz and Pişkin 2006) for rat the trigone, and 10^{-2} M (Noble et al. 1997) for human prostate tissue. The reason for the difference between effective concentrations of phenylephrine can be due to the density and distribution of adrenergic receptors in the tissues and it may vary in different organs and types.

Alfuzosin is selective for α_1 receptors versus α_2-adrenoceptors but without α_1 subtype selectivity (Davey 1987). There are many studies related to alfuzosin hydrochloride *in vivo* and *in vitro*. Giuliano et al. (2004) stated that alfuzosin given intravenously to rats block contractions occurring on smooth muscle of seminal vesicle and bladder neck. In a cat model, the elevated urethral pressure which occurs via sympathetic nerve stimulation or infusion of phenylephrine was significantly inhibited by alfuzosin, while no sustained elevation of blood pressure was observed. In comparison to prazosin and terazosin, it exerted the highest selectivity for the lower urinary tract (Mátyus and Horváth 1997).

De Reijke and Klarskov (2004) stated that improving symptoms belonging to prostate patients who use alfuzosin are lower in comparison to doxazosin. Palea and Barras (2003) determined that contractions occurring in the rabbit corpus cavernous were blocked by alfuzosin. Lefevre-Borg et al. (1993) informed that contractions induced by phenylephrine in the rabbit trigone smooth muscle and urethra were blocked by prazosin at an equal rate, whereas alfuzosin strongly decreased urethra contractions when compared with the trigone. The amplitudes of contractions caused by electrical stimulation in the presence of phenylephrine plus alfuzosin (10^{-8} M, 10^{-7} M, 10^{-6} M, 10^{-5} M) were numerically lower than phenylephrine treatment alone (Fig. 1, Table 2).

In our study, we showed that the responses of only phenylephrine treatments compared with the responses of phenylephrine plus alfuzosin significantly decreased by 7% at a 10^{-8} M concentration, 14% at a 10^{-7} M concentration, 20% at a 10^{-6} M concentration and 29% at a 10^{-5} M concentration, respectively. It was concluded that contractions occurring in the rabbit trigone smooth muscle could be less strongly prevented by alfuzosin than by the other two antagonists. This result may be due to the non-selective feature of alfuzosin for alpha adrenergic receptors in the rabbit trigone.

Subtype non-selective α_1-adrenoceptor antagonist such as doxazosin which was originally developed for hypertension has been used for the treatment of BPF. This agent was shown to be effective, but it may cause orthostatic hypotension because of the existence of α_1-adrenoceptors in the vasculature (Chapple 1994). Alabaster and Davey (1986) and Davey (1987) stated in the studies done on the isolated aortic ring of rabbit, brain membranes and venues of dogs that affinity of doxazosin for α_1-adrenergic receptors was higher than its affinity for α_2-adrenergic receptors. Also *in vivo* studies concluded that blood pressure and contractions of the rat bladder decreased as a result of giving doxazosin intraspinally to rats (Yoshiyama et al. 2000; Jeong and Lee 2000), intravenously to cats (Ramage and Wyllie 1995) and dogs. This proved that doxazosin has an antagonist effect for α_1-adrenergic receptors.

The amplitudes of contractions caused by electrical stimulation of phenylephrine plus doxazosin (10^{-7} M, 10^{-6} M, 10^{-5} M) were numerically lower ($p < 0.05$) than phenylephrine treatment alone (Fig. 1 and Table 2). This fact showed that all concentrations of doxazosin dose-dependently inhibited the contractions originating from noradrenalin in the rabbit trigone smooth muscle. In the study, when compared with the only effective dosage of phenylephrine, the responses taken to phenylephrine in the presence of all concentrations of doxazosin decreased by 22% in 10^{-7} M concentration, 30% in 10^{-6} M concentration and 38% in 10^{-5} M concentration, respectively. This result showed that contractions occurring as a result of the action of phenylephrine in the rabbit trigone smooth muscle and α_1 adrenergic receptors could be prevented by the increase in density of doxazosin. Seo et al. (1999) stated that 10% the inhibition ratio of contraction were induced by doxazosin in rabbit trigone and cavernous tissues. At the same time Koç (2001) informed that doxazosin had a pressing effect on the contractions occurring after noradrenalin in the rat vas deferens, seminal vesicle and epididymis smooth muscles. These findings proved that doxazosin had an α_{1a} adrenergic receptor antagonist effect. This result suggested that α_{1a} adrenergic receptors at rabbit bladder trigone smooth muscle could be prevented by doxazosin; therefore the flow of urine could be eased by loosening the neck part of the bladder.

Tamsulosin, a phenylethylamine type a-blocker, has a high affinity for alpha-1 adrenoceptor with moderate selectivity. This selectivity is also preserved for its metabolites indicating that it is encoded to the phenoxy ring moiety (Lyseng-Williamson et al. 2002). In the study, when compared with the responses of the only usage of phenylephrine, contractions occurring after phenylephrine in the presence of all contentrations starting from the lowest concentration of tamsulosin decreased by 31% in 10^{-7} M concentration, 39% in 10^{-6} M concentration and 48% in 10^{-5} M concentration, respectively. This showed

that contractions occurred as a result of the action of phenylephrine on the α_1 adrenergic receptors in the rabbit trigone smooth muscle, and the contractions could be prevented by increasing the concentration of tamsulosin. This fact indicated that tamsulosin dose-dependently inhibited the contractions caused by noradrenalin in the rabbit bladder trigone smooth muscle ($p < 0.05$) (Fig. 1 and Table 2).

Some researchers found that the contractions of *in vivo* dog (Breslin et al. 1993; Kenny et al. 1994; Kontani and Shiraoya 2002 and *in vitro* rat (Tang et al. 2004) prostate smooth muscle induced by epinephrine and phenylephrine could be prevented by tamsulosin. Moreover, the contractions occurring due to phenylephrine in the human prostate smooth muscle could be blocked by tamsulosin (Bouchelouche et al. 2005; Harada and Fujimura (2000), and tamsulosin is used in the treatment of illnesses related to the human prostate and lower urinary tracts (Kawachi 1998; Akduman and Crawford 2001; Schulman et al. 2001; Kirby 2003).

Some researchers stated that the contractions occurring after phenylephrine in the dog bladder could be prevented by tamsulosin competitively (Testa et al. 1997; Minneman et al. 1988; Leonardi et al. 1997; Witte et al. 2002); furthermore, the effects of tamsulosin on the amplitude and frequency of contractions in the rat bladder was low (Sudoh et al. 1997). In previous studies, contractions of the rat tail (Lachnit et al. 1997; Jähnichen et al. 2004) and mesenteric artery (Van Der Graaf et al. 1996) induced by phenylephrine or noradrenalin were more strongly prevented by tamsulosin than by other alpha adrenergic antagonists, such as prazosin, phentholamin, WB-401, 5 methil-urapidil, spiperone and HV 723.

Seo et al. (1999) informed that tamsulosin prevented the contractions occurring after phenylephrine in the rabbit cavernous smooth muscle 1 000 × more than doxazosin and terazosin. These authors found 81% inhibition induced by tamsulosin in the rabbit trigone smooth muscle. Our result is similar to the above finding, with contractions decreased only by 48%. This may be due to the density of receptors in tissues or differences between species.

In this study, as a result of stimulating adrenergic receptors by phenylephrine we found that tamsulosin could prevent the contractions occurring in the trigone area more strongly than alfuzosin and doxazosin, as a result of the selective affinity of tamsulosin for α_{1a} adrenergic receptors. Potentially, tamsulosin may allow the control of benign prostate hyperplasia with its minimal adverse effect on other alpha-adrenergic receptors (e.g., low potential for interfering with blood pressure control, vasodilatation).

Our experiment comparing the effect of relatively selective (tamsulosin) and non-selective (alfuzosin and doxazosin) alpha-1 adrenergic receptor antagonists on relaxation of the rabbit trigonal smooth muscle demonstrated that tamsulosin was the most effective drug. Therefore, alfuzosin hydrochloride, doxazosin mesylate and tamsulosin hydrochloride could provide an easy flow of urine by inhibition of alpha adrenergic receptors in cat and dog diseases; however, it was decided that these effects must be supported by clinical studies.

Účinek alfa$_1$-adrenergních antagonistů (alfuzosin, doxazosin a tamsulosin) na relaxaci hladkého svalu z trigonum vesicae králíka

Autoři zkoumali vliv alfuzosinu, doxazosinu a tamsulosinu *in vitro* na hladký sval z trigonum vesicae králíka. V pokusech bylo použito 15 králíků o hmotnosti 2,5-3 kg. Z každého izolovaného močového měchýře byl odpreparován proužek svalu ve tvaru trigona. Každý segment byl zpočátku vystaven tahu 1g a za stálého probublávání 95% O_2 a 5% CO_2 bylo dosaženo rovnováhy svalové tense. Poté byla stanovena intenzita elektrická stimulace, která vyvolala submaximální svalovou kontrakci, a aplikací různých koncentrací fenylefrinu (postupně 10^{-8} M, 10^{-7} M, 10^{-6} M, 10^{-5} M) byly stanoveny jeho účinné dávky pro zkoumané trigony.

Poté byla aplikována 10^{-8} M dávka alfuzosinu, po 20 min byla do roztoku přidána účinná dávka fenylefrinu (10^{-5} M). Po dalších 7 min byl aplikován elektrický stimul, který vyvolal svalovou kontrakci. Po provedení stimulace byla tkáň dvakrát propláchnuta v intervalu 2 min a ponechána v klidu, dokud se nevrátila do původního stavu. Proces byl postupně opakován i s ostatními dávkami alfuzosinu (10^{-7}M, 10^{-6}M, 10^{-5}M), doxazosinu (10^{-7}M, 10^{-6}M, 10^{-5}M) a tamsulosinu (10^{-7}M, 10^{-6}M, 10^{-5}M).

Srovnání amplitud odezvy na všechny použité koncentrace doxazosinu, alfuzosinu a tamsulosinu na hladký sval trigonum vesicae s amplitudou odezvy účinné koncentrace fenylefrinu, vedlo k zjištění, že kontraktilita byla po podání tamsulosin hydrochloridu vyšší než po podání alfuzosin hydrochloridu a doxazosin mesylátu. Bylo tak prokázáno, že alfuzosin, doxazosin a tamsulosin inhibují kontrakce vyvolané účinkem noradrenalinu na hladký sval trigonum vesicae králíka. Výsledky studie lze využít pro další studie jak *in vitro,* tak *in vivo.*

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