

Comparative effect of alfuzosin and tamsulosin on the contractile response of isolated rabbit prostatic and iris dilator smooth muscles

Possible model for intraoperative floppy-iris syndrome

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PURPOSE: To compare the pharmacologic properties of tamsulosin and alfuzosin in isolated prostatic and iris dilator smooth muscle from pigmented rabbits.

SETTING: UROsphere Laboratories, Université Paul Sabatier, Toulouse, France.

METHODS: Prostatic and iris dilator smooth muscle strips were placed in organ baths. A concentration-response curve to phenylephrine was compared before and after incubation with tamsulosin or alfuzosin.

RESULTS: Both drugs were approximately 30 times less potent in iris dilator than prostatic smooth muscle. In the iris, tamsulosin acted as a competitive antagonist starting at the 0.03 μM concentration ($pA_2 = 7.96$). This is in the same range as the maximum plasma concentration after a 0.4 mg dose of tamsulosin in humans (0.025 μM). The antagonistic effect of alfuzosin in the iris was weaker (calculated mean pA_2 value of 5.63 ± 0.19). Concentrations with an equipotent antagonistic effect on rabbit iris dilator muscle (3.0 and 10.0 μM) were approximately 100 to 300 times higher than the maximum plasma concentrations after a 10.0 mg dose of alfuzosin in humans (0.032 μM).

CONCLUSIONS: Tamsulosin was more effective than alfuzosin at blocking adrenergic contraction of the iris dilator muscle in pigmented rabbits. Both drugs were less potent in the iris than in the prostate, which suggests that an additional iris receptor could be involved. If valid in humans, our results suggest that attainable plasma concentrations of tamsulosin are able to antagonize iris dilator smooth muscle contraction, whereas those of alfuzosin are not. This could explain the higher frequency of intraoperative floppy-iris syndrome in patients treated with tamsulosin than with alfuzosin.

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Since it was first reported in 2005 by Chang and Campbell,¹ intraoperative floppy-iris syndrome (IFIS) has become a major concern for cataract surgeons. This small-pupil syndrome of variable severity is most commonly associated with tamsulosin, a systemic α_1 -adrenoceptor (α_1 -ADR) blocker that is selective for the α_{1a} -receptor subtype that predominates in the prostate. The uroselectivity resulting from this subtype specificity has made tamsulosin the most commonly prescribed medication for the lower urinary tract symptoms of benign prostatic hyperplasia (BPH).² Severe IFIS is characterized by iris billowing, iris prolapse, and progressive intraoperative miosis.¹ Poor preoperative pupil dilation is common.¹ The intraoperative iris behavior is consistent with deficient

iris dilator smooth muscle tone, caused by the systemic α_1 -ADR antagonist.¹

Retrospective studies affirm that when the surgeon is not anticipating IFIS, the unexpected iris prolapse and miosis increase the rate for surgical complications such as posterior capsule rupture.³⁻⁵ Unfortunately, simply stopping tamsulosin does not seem to reduce the incidence or severity of IFIS.^{1,4} However, when the surgeon is forewarned of the likelihood of IFIS by the medication history, specific surgical strategies can be used.⁴ The high prevalence of BPH and cataracts in aging men makes IFIS secondary to systemic α_1 -ADR antagonists a significant problem for cataract surgeons and their patients.

Chang and Campbell¹ reported a strong association between IFIS and tamsulosin but could not retrospectively identify cases of iris prolapse in patients taking nonspecific α_1 -ADR blockers. Although subsequent experience has shown anecdotally that IFIS can occur in association with nonspecific α_1 -ADR blockers, the severity and frequency are not as severe as with tamsulosin.⁵⁻⁹ A recent retrospective study⁵ comparing the rates of IFIS in tamsulosin and alfuzosin patients shows that the incidence of IFIS with alfuzosin, a non-subtype-selective α_1 -ADR antagonist, was significantly lower. Since alfuzosin also demonstrates clinical uroselectivity, this finding has important ramifications for the pharmacologic treatment of BPH in patients who might later have cataract surgery.

About 70% of α_1 -ADR in the human prostate are of the α_{1a} subtype.¹⁰ Recent studies demonstrate that the α_{1a} -ADR subtype, activated by phenylephrine (PE), also mediates iris dilator muscle contraction and mydriasis in rats¹¹ and rabbits.¹² It might therefore be expected that other α_1 -ADR antagonists used for the treatment of BPH, such as alfuzosin, would inhibit iris dilator smooth muscle contraction, causing IFIS with a frequency and severity equal to the frequency and severity with tamsulosin. The reason behind the clinical finding of a much stronger association of IFIS with tamsulosin has not been explained.⁵⁻⁹ The pharmacology of α_1 -ADR antagonists such as tamsulosin and alfuzosin in the iris has not been examined experimentally.

This study compared the antagonistic properties of tamsulosin and alfuzosin on PE-induced contractions in isolated prostatic and iris dilator smooth muscle from male rabbits. The investigations were performed in pigmented rabbits because a previous study showed similar α_1 -ADR pharmacology in humans and pigmented rabbits compared with albino rabbits.¹³

MATERIALS AND METHODS

Male pigmented rabbits (CEGAV) were killed and exsanguinated. Both eyes and the ventral prostate were immediately dissected and placed in oxygenated Krebs solution with the

following composition (in millimolars): NaCl 114, KCl 4.7, CaCl₂ 2.5, MgSO₄ 1.2, KH₂PO₄ 1.2, NaHCO₃ 25, glucose 11.7 (pH 7.4, gassed with 95% O₂ and 5% CO₂ at 37°C). Propranolol (1.0 μ M), desipramine (0.1 μ M), deoxycorticosterone (3.0 μ M), and atropine (1.0 μ M) were added to the Krebs-Henseleit solution to block β -ADRs, neuronal and extraneuronal monoamine reuptake, and muscarinic receptors, respectively. Contractile responses were measured using isometric tension transducers (type IT-1, EMKA Technologies) and recorded using a data acquisition system (MacLab 8e). For prostate and iris, N-nitro-L-arginine methyl ester (L-NAME) was added to organ baths at the final concentration of 0.1 mM for 30 minutes before the first and second concentration-response curve (CRC) to the α_1 -ADR agonist PE was performed.

Protocol 1 (Prostatic Smooth Muscle)

Transverse preparations of the prostate were suspended vertically in 25 mL glass organ baths under a loading tension of 1g. After 60 minutes of equilibration, the smooth muscle strips were exposed to 30 μ M PE to measure their viability. Strips having a contractile response of less than 0.5 g were discarded. Following a 30-minute washout period, the first CRC to PE (control curve) was obtained using sequential half-log unit concentration increments (range 0.1 to 100 μ M) until the maximum contractile response was reached. Following a 60-minute washout period, tissues were incubated for 60 minutes with tamsulosin (0.001, 0.003, 0.01, 0.1 μ M sequential concentration increments), alfuzosin (0.1, 0.3, 1.0 μ M), or the inactive solvent before the second CRC to PE (treatment curve) was obtained. Only 1 antagonist concentration was tested on each single tissue.

Protocol 2 (Iris Dilator Muscle)

Under a surgical microscope, iris was dissected in ice-cold oxygenated Krebs solution. A strip of iris dilator muscle (approximately 2.0 mm wide and 4.0 mm long) was carefully isolated and mounted vertically in a 5 mL glass organ baths under an initial tension of 50.0 mg. After 90 minutes of equilibration, the smooth muscle strip was exposed to 30.0 μ M PE to measure viability. Following a 30-minute washout period, the first cumulative CRC to PE (control curve) was obtained using sequential half-log unit concentration increments (range 0.1 to 100 μ M) until the maximum contractile response was reached. Following a 60-minute washout period, the tissues were incubated for 60 minutes with tamsulosin (0.01, 0.03, 0.1, 1.0 μ M), alfuzosin (3.0, 10.0, 30.0 μ M) or the inactive solvent before the second PE CRC (treatment curve) was obtained. Only 1 antagonist concentration was tested on each single tissue.

Analysis and Expression of Results

Data are expressed as mean \pm SEM. The contractile responses to PE in the absence and presence of the antagonist (first and second CRC) were expressed as the percentage of the initial contraction induced by 30.0 μ M PE.

Using mean values, CRCs to PE were fitted by nonlinear regression using the GraphPad Prism version 4.0 software to obtain the following parameters: (1) Emax = maximum contraction induced by PE; (2) EC₅₀ = PE concentration, which induces 50% of the maximum effect, expressed as pEC₅₀ (-log EC₅₀). Mean CRCs for the control and treated strips were fit in parallel and statistically compared. The first

Table 1. Estimated Log EC₅₀ values (with 95% confidence intervals) obtained on control curves for phenylephrine (before and after incubation with the solvent for tamsulosin and alfuzosin) on the rabbit isolated prostatic and iris dilator smooth muscles.

Tissues	Tamsulosin Groups			Alfuzosin Groups		
	Log EC ₅₀ (95% C.I.)		N° Strips	Log EC ₅₀ (95% C.I.)		N° Strips
	Before Solvent	After Solvent		Before Solvent	After Solvent	
Prostate	5.32 (5.43–5.21)	5.21 (5.32–5.10)	7	5.20 (5.37–5.04)	5.20 (5.37–5.04)	6
Iris dilator	4.93 (5.23–4.62)	4.97 (5.28–4.67)	7	5.10 (5.47–4.74)	5.15 (5.50–4.79)	5

fit was used to compare Emax values for the control and treatment response curves. If these values were not statistically different, a second fit was performed matching Emax to obtain pEC₅₀ values for each pair of curves. Differences were considered statistically significant when the null hypothesis was rejected at a risk α of less than 0.05.

Finally, dose ratios (ratios of pEC₅₀ values for PE in the presence and absence of tamsulosin or alfuzosin) were calculated and used to estimate antagonist potency (pA₂ or pK_B value). The pA₂ value is the negative logarithm to the base 10 of the molar concentration of the antagonist that makes it necessary to double the concentration of the agonist to elicit the same response obtained in the absence of the antagonist.¹⁴ The pA₂ value is calculated by using a linear regression plot [log (dose ratio – 1)] versus [log antagonist concentrations] used. This classic method is called Schild plot.

Chemicals

Tamsulosin and alfuzosin were obtained from Sanofi-Aventis. Propranolol hydrochloride, desipramine hydrochloride, deoxycorticosterone acetate, atropine sulfate salt hydrate, L-NAME, and (R)-(-)-phenylephrine hydrochloride were obtained from Sigma-Aldrich.

Deoxycorticosterone acetate was dissolved in dimethylsulphoxide. All other compounds were dissolved in distilled water. All dilutions were prepared in distilled water. For each compound, fresh solutions were prepared for each day of experimentation.

RESULTS

Antagonism of Phenylephrine-Induced Contractions in Prostatic Smooth Muscle

After the first CRC to PE was obtained, some tissues were incubated for 60 minutes with the solvent used to dissolve alfuzosin and tamsulosin (distilled water). This treatment had no effect on the second CRC to PE, suggesting that incubation with distilled water had no inhibitory effects on PE contractility. This was demonstrated by the similar Emax and EC₅₀ values obtained in the first and second CRCs in the presence of vehicle (Table 1; Figures 1, A, and 2, A).

This preliminary experiment was necessary to confirm the absence of confounding factors such as depression of the second CRC to PE following vehicle incubation, which would be incompatible with our

experimental protocol for testing alfuzosin and tamsulosin using 2 CRCs to PE in the same tissue.

At concentrations of 0.001, 0.003, and 0.01 μ M, tamsulosin antagonized the CRC to PE in a concentration-dependent manner without affecting Emax values (Figure 1, B–D). At 0.1 μ M, tamsulosin largely depressed the Emax value of PE (Figure 1, E), which made it impossible to calculate the corresponding dose ratio with respect to the control curve. The antagonist potency (pA₂) value for tamsulosin was estimated as 9.11 by the Schild plot (Figure 3, A). The Schild plot slope was much greater than unity

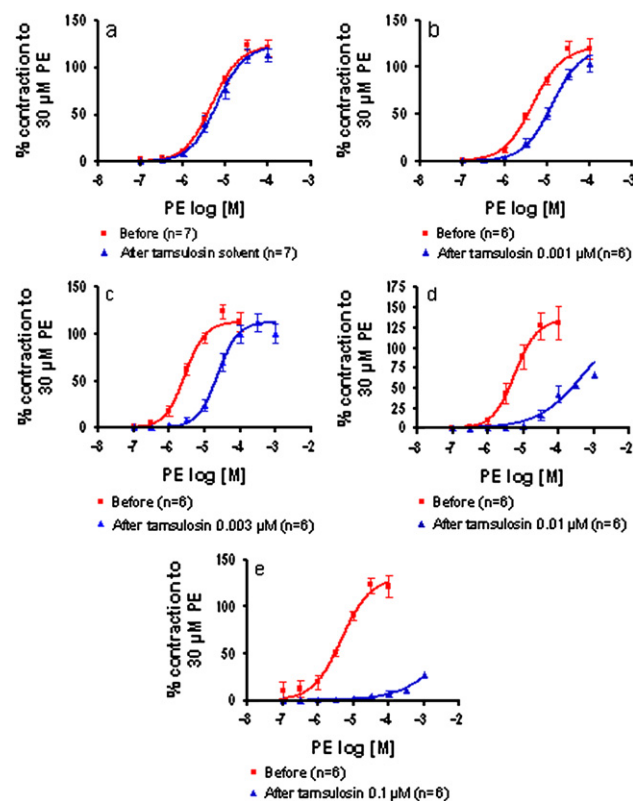


Figure 1. Effect of PE after incubation with solvent (A) or different concentrations of tamsulosin at 0.001 μ M (B), 0.003 μ M (C), 0.01 μ M (D), and 0.1 μ M (E) on rabbit isolated prostatic smooth muscle.

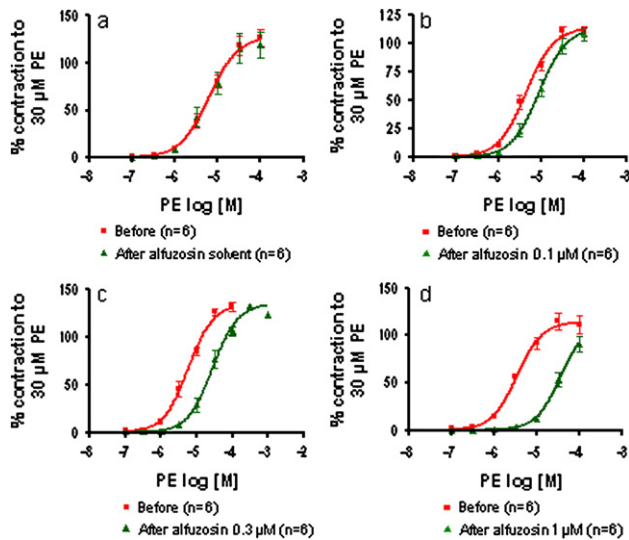


Figure 2. Effect of PE after incubation with solvent (A) or different concentrations of alfuzosin at 0.1 μ M (B), 0.3 μ M (C), and 1 μ M (D) on rabbit isolated prostatic smooth muscle.

(1.67 ± 0.27), indicating a noncompetitive antagonism. Dose ratios used for the linear regression are shown in Table 2.

At concentrations of 0.1, 0.3, and 1.0 μ M, alfuzosin antagonized the CRC to PE in a concentration-dependent manner without affecting E_{max} values (Figure 2, B–D). The pA_2 value for alfuzosin found by linear regression was 7.03 (Figure 3, B), which was 2 orders of magnitude lower than the tamsulosin pA_2 value. In contrast to that for tamsulosin, the Schild plot slope for alfuzosin was close to unity (0.99 ± 0.09), indicating pure competitive antagonism.

Antagonism of Phenylephrine-Induced Contractions in Iris Dilator Smooth Muscle

Paralleling what was observed in the prostate, the 2 consecutive CRCs to PE were reproducible in the same tissue. This was demonstrated by the similar E_{max} and EC_{50} values obtained in the first and second

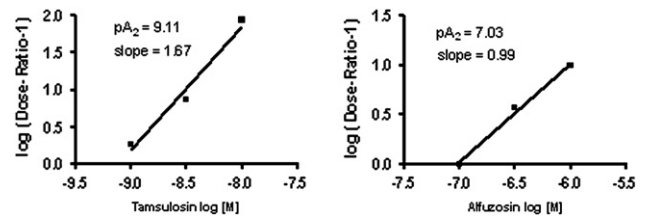


Figure 3. Schild plots for tamsulosin and alfuzosin on the PE-induced contractions in rabbit isolated prostatic smooth muscle.

CRCs in the absence of the test drug (Table 1; Figures 4, A, and 5, A).

Tamsulosin had a low antagonistic effect at the lowest concentration tested (0.01 μ M) (Figure 4, B); statistical analysis showed that the EC_{50} values in the presence (4.84 ± 0.16) and absence (5.02 ± 0.16) of 0.01 μ M tamsulosin were not statistically different ($P = .06$).

At concentrations of 0.03, 0.1, and 1.0 μ M, tamsulosin antagonized the CRC to PE in a concentration-dependent manner without affecting E_{max} values (Figure 4, C–E). The antagonist potency (pA_2) value was equal to 7.96, and the Schild plot slope was 0.89 ± 0.05 (Figure 6, A). Dose ratios used for the linear regression (Schild plot) are shown in Table 2.

At concentrations of 3.0, 10.0, and 30.0 μ M, alfuzosin antagonized the CRC to PE in a concentration-dependent manner without affecting E_{max} values (Figure 5, B–D). The antagonist potency value found by linear regression was 6.39 (Figure 6, B), but the Schild plot slope was different from unity (0.45 ± 0.36). This result indicates that alfuzosin is not a competitive antagonist of the receptor activated by PE in the rabbit iris dilator muscle. Therefore, the Schild plot method could not be used to calculate alfuzosin potency. Instead, a mean of single pA_2 values obtained with each of the 3 concentrations of alfuzosin was calculated, resulting in a pA_2 value of 5.63 ± 0.19 . Dose ratios for the 3 concentrations of alfuzosin are shown in Table 2.

Table 2. Dose ratios and pA_2 values obtained for tamsulosin and alfuzosin on the rabbit isolated prostatic and iris dilator smooth muscles.

Tissue	Alfuzosin		Tamsulosin	
	Dose Ratio (μ M)	pA_2	Dose Ratio (μ M)	pA_2
Prostate (N=6 rabbits)	2.00 (0.1)	7.03	2.86 (0.001)	9.11
	4.77 (0.3)		8.34 (0.003)	
	10.88 (1)		88.4 (0.01)	
Iris dilator (N=6 rabbits)	4.22 (3)	6.01	3.38 (0.01)	7.96
	3.65 (10)	5.42	8.82 (0.1)	
	10.2 (30)	5.46	53.9 (1)	
Mean \pm SEM		5.63 \pm 0.19		

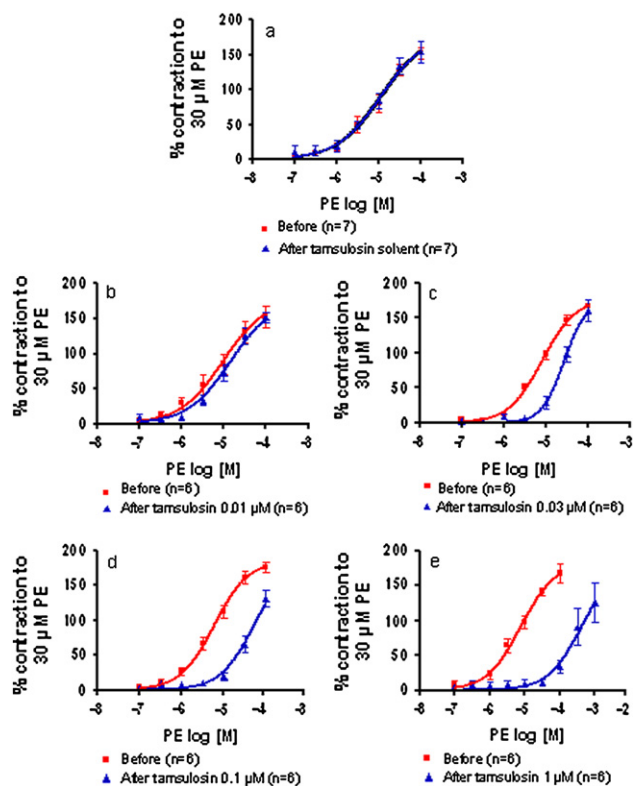


Figure 4. Effect of PE after incubation with solvent (A) or different concentrations of tamsulosin at 0.01 μM (B), 0.03 μM (C), 0.1 μM (D), and 1.0 μM (E) on rabbit isolated iris dilator muscle.

DISCUSSION

Several retrospective studies confirm a higher risk for surgical complications in eyes with IFIS.^{1,3-5} Besides tamsulosin, nonspecific α_1 -ADR antagonists have been associated with IFIS.⁵⁻⁹ However, several clinical studies show that IFIS is more strongly associated with tamsulosin than with non-subtype-specific α_1 -ADR antagonists such as alfuzosin. In a prospective study of 1786 patients, Chadha et al.⁶ report that IFIS occurred in 57% of patients taking tamsulosin but in only 2% of those taking nonspecific α_1 -ADR antagonists. In a prospective study of 1968 patients, Oshika et al.⁹ report IFIS in 43% of patients taking tamsulosin compared with 19% of patients taking naftopidil, a nonselective α_1 -ADR antagonist.

In a retrospective chart review of 1298 cataract patients, tamsulosin accounted for only 26% of the α -blockers used but 71% of the cases with intraoperative iris prolapse (S.B. Radomski, et al, "Intraoperative Iris Prolapse During Cataract Surgery in Men Using Alpha-Blockers for Lower Urinary Tract Symptoms due to Benign Prostatic Hypertrophy," presented at the annual meeting of the American Urological Association, Atlanta, Georgia, USA, May 2006. Abstract available at: http://www.urotoday.com/287/conference_reports/

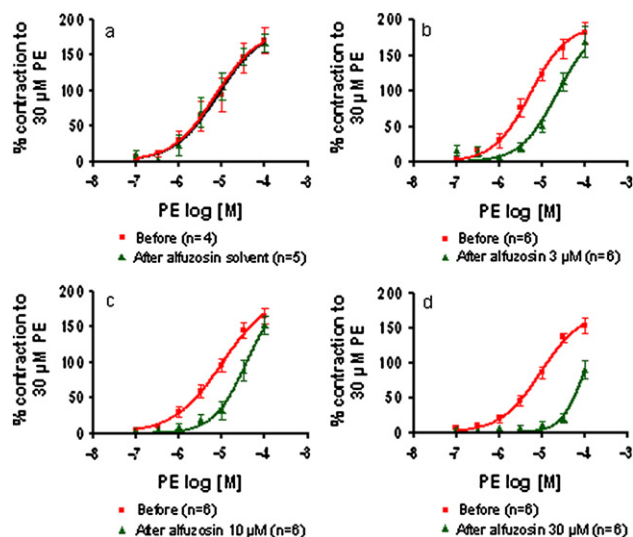


Figure 5. Effect of PE after incubation with solvent (A) or different concentrations of alfuzosin at 3.0 μM (B), 10.0 μM (C), 30.0 μM (D) on rabbit isolated iris dilator muscle.

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Alfuzosin, similar to tamsulosin, is a uroselective drug for BPH that is less likely to cause postural hypotension than other nonspecific α_1 -ADR blockers.¹⁵ Knowledge that one drug is less likely to cause IFIS would have a significant impact on prescribing patterns for BPH patients with cataracts. Why tamsulosin should be more likely to cause IFIS than nonspecific α_1 -antagonists is unknown. Although the pharmacology of both tamsulosin and alfuzosin has been well studied in the prostate, the action of these agents in the iris dilator muscle has not been examined experimentally.

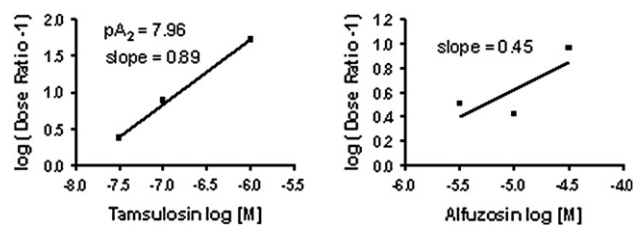


Figure 6. Schild plots for tamsulosin and alfuzosin on the PE-induced contractions in rabbit isolated iris dilator muscle.

In our study using rabbit prostatic smooth muscle, alfuzosin behaved as a competitive antagonist, as indicated by the Schild plot slope that was very close to unity. The antagonistic potency of alfuzosin in prostatic strips from pigmented rabbits ($pA_2 = 7.03$) is quite similar to that reported in prostatic strips from albino New Zealand rabbits ($pA_2 = 7.25$).¹⁶ In contrast, tamsulosin acted as a noncompetitive antagonist and almost abolished the PE response at a 0.1 μ M concentration. The antagonistic potency of tamsulosin in prostatic strips from pigmented rabbits (9.11) is similar to that obtained in binding studies on cloned rabbit α_{1a} -ADRs (9.40).¹⁷ On this basis, we conclude that PE-induced contraction of prostatic smooth muscle in pigmented rabbits is mediated by α_1 -ADRs. These are most likely the α_{1a} -ADR subtype, as previously claimed.¹⁸

In the rabbit iris dilator muscle, alfuzosin was not a competitive antagonist, as indicated by the flat Schild plot slope. Moreover, alfuzosin's potency for antagonizing PE-induced contraction in the iris dilator muscle appears to be low. This result was unexpected and, to our knowledge, has not been described for alfuzosin in any other tissue where α_1 -mediated muscle contraction takes place. According to quantitative receptor pharmacology,¹⁹ Schild plot slopes less than unity can unveil receptor heterogeneity, whereby the agonist induces a response by activating more than one receptor subtype. Therefore, we postulate that PE-induced contractions in the isolated rabbit iris dilator smooth muscle could be mediated by the activation of 2 receptors— α_1 -ADR and another unidentified receptor.

To explain our results, alfuzosin would have to display a much lower affinity for this hypothetical second receptor than for α_1 -ADR. This is because alfuzosin was 30 times less potent at blocking PE-induced contraction in iris tissue than it was in prostatic tissue. This should be impossible if PE-induced contraction was mediated exclusively by α_1 -ADR in both tissues. The unexpected presence of a hypothetical second receptor is further supported by the observation that tamsulosin was 10 to 30 times less potent in the rabbit iris than in the rabbit prostate, where α_1 -ADR mediation is well understood. Moreover, tamsulosin's antagonistic potency in the rabbit iris dilator muscle is approximately 100 times less than its antagonistic potencies for the 3 cloned α_1 -ADR subtypes.²⁰

Our study does not support the conclusions of a previous investigation performed in anesthetized Japanese white rabbits,²¹ showing that several α_1 -ADR antagonists, including tamsulosin and alfuzosin, inhibited PE-induced mydriasis in the same dose range as they inhibited PE-induced elevation of intraurethral pressure. However, this study in albino rabbits may not be relevant to human pharmacology. Ishikawa

et al.¹³ reported that 5-methylurapidil, a well-known α_{1a} -ADR antagonist, exhibited different antagonist potencies (pK_B values) in albino rabbits (8.3), pigmented rabbits (6.4), and human iris (6.6).

The difference in receptor pharmacology between pigmented and albino rabbits is further supported by our data showing that tamsulosin potency in iris dilator smooth muscle from pigmented rabbits ($pA_2 = 7.96$) was much lower than that previously observed in albino rabbits ($pA_2 = 9.73$),²² confirming results obtained with 5-methylurapidil.¹³ On the basis of these comparisons, we conclude that the α_1 -ADR pharmacology of the human iris appears to more closely resemble that of the pigmented rabbit iris than the albino rabbit iris.

The nature of the hypothetical receptor activated by PE in the iris dilator muscle of pigmented rabbits is a matter of speculation. It is known that tamsulosin is a potent ligand of rat native 5-hydroxytryptamine (5-HT)_{1A} and D₂ receptors, while alfuzosin has a very low affinity ($pK_i < 5.0$) for these same receptors.²⁰ The possible importance of 5-HT_{1A} and D₂-like receptors in the occurrence of IFIS has not been studied. However, there is some clinical evidence that drugs affecting 5-HT function induce pupil changes in humans. Fenfluramine, which releases 5-HT from synapses,²³ and the 5-HT reuptake inhibitor indalpin²⁴ can cause mydriasis in humans. The 5-HT_{1A} receptor agonist, 8-OH-DPAT, induces mydriasis in anesthetized rats.²⁵ Ocular dopaminergic activity has not been fully elucidated, but there is some evidence that D₂ and D₃ receptors are present in the terminals of postganglionic sympathetic nerves in the anterior segment of the eye.^{26,27} Moreover, it was recently reported that D₂ receptor antagonists such as chlorpromazine, haloperidol, droperidol, and metoclopramide block reflex pupil dilation and induce miosis during general anesthesia.²⁸

Regardless of the receptor involved, *in vitro* differences between alfuzosin and tamsulosin in their selectivity and affinity for it might explain certain *in vivo* differences. For example, tamsulosin impairs bulbospongiosus muscle contractions induced by central injection of 8-OH-DPAT in anesthetized rats while alfuzosin does not. This finding may be explained by a greater affinity of tamsulosin than of alfuzosin for 5-HT_{1A} and D₂-like receptors.^{29,30}

Taken together, our results and hypotheses could explain why IFIS is more commonly associated with tamsulosin than with alfuzosin. The reduced antagonistic potency of both drugs in the rabbit iris dilator muscle compared with that in the prostatic smooth muscle could be explained by a lower affinity for a hypothetical second iris receptor compared with the α_1 -AR. If one assumes that an unidentified second iris

dilator muscle receptor exists, additional pharmacologic differences between tamsulosin and alfuzosin become relevant. The finding that tamsulosin was a more powerful antagonist of rabbit iris dilator muscle contraction than alfuzosin *in vitro* could be explained by a higher affinity of tamsulosin for this hypothetical second receptor.

Finally, it is interesting to compare alfuzosin and tamsulosin antagonistic concentrations used *in vitro* in rabbits to plasma and prostatic tissue levels of these drugs measured *in vivo*. In healthy human volunteers, the 10 mg recommended daily BPH treatment dose of alfuzosin produced a maximum plasma concentration (C_{max}) of 13.6 ng/mL \pm 5.6 (SD) [SmPC Uroxatral]. This corresponds to a tissue concentration of 0.032 μ M. This level is 100 to 300 times less than the concentration having a minimum antagonistic effect on the rabbit iris dilator muscle (3.0 to 10.0 μ M; DR = 4.22 and 3.65, respectively) in our experiments. On the other hand, 0.4 mg tamsulosin tablets in men produced a C_{max} value of 11 ng/mL (SmPC Omixel LP 0.4 mg), which corresponds to a 0.025 μ M tissue level. This approximates the same concentration (0.03 μ M) that had an antagonistic effect on the iris dilator muscle (DR = 3.38) in our study. If these animal results were applicable to the human iris, the C_{max} typically attainable with tamsulosin would be sufficient to block contraction of the iris dilator muscle, whereas the typical C_{max} of alfuzosin would not.

In conclusion, in pigmented rabbits, both tamsulosin and alfuzosin are less potent at blocking smooth muscle contraction in the iris than in the prostate. This suggests that in the pigmented rabbit iris, PE-induced dilator muscle contraction is mediated by more than one receptor, and not solely by the α_1 -AR. The relatively greater ability of tamsulosin to antagonize iris dilator contraction compared with alfuzosin could be explained by differences in affinity for this unidentified second iris receptor. That tamsulosin shows an antagonist effect on 5-HT_{1A} and D₂/D₃ receptors while alfuzosin does not may also play a role. Finally, if valid in humans, our results suggest that plasma concentrations of tamsulosin are able to antagonize the iris dilator smooth muscle, whereas those of alfuzosin are too low to have an antagonist effect. This could explain why tamsulosin appears to be more strongly associated with IFIS than alfuzosin. Well-designed clinical trials are needed to further evaluate these hypotheses.

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