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Effects of α_1-adrenoceptor antagonists on agonist and tilt-induced changes in blood pressure: relationships to uroselectivity

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Abstract

We evaluated the uroselectivity of a series of α_1-adrenoceptor antagonists by comparing their potency against phenylephrine-induced increases in urethral perfusion pressure and diastolic blood pressure in the anesthetized rabbit and pithed rat. In the rabbit, Rec 15/2739 (*N*-[3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl]-3-methyl-4-oxo-2-phenyl-4*H*-1-benzopyran-8-carboxamide) as well as analogs with a chlorine substituent on the methoxyphenyl ring (Rec 15/2869) or this substituent combined with the replacement of the phenyl substituent on the pyran ring by cyclohexyl (Rec 15/3011) were 2–6-fold more potent against the urethral vs. vascular response to phenylephrine. Rec 15/2841 (*N*-[3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl]-3-methyl-4-oxo-2-cyclohexyl-4*H*-1-benzopyran-8-carboxamide) was only 1.5-fold more potent against the urethral response. SL 89.0591 and tamsulosin also showed selectivity for the urethral response (2–2.5-fold), while the quinazolines produced equipotent blockade of urethral and vascular responses (selectivity ratio = 0.9–1.1). The urethral selectivities of Rec 15/2739 and its derivatives were confirmed by evaluation of the response to tilt in sedated, hypovolemic rabbits. Phenylephrine challenge assays did not show any of the antagonists, with the exception of terazosin at 300 μg kg^{-1}, to be uroselective in the rat (selectivity ratios = 0.2–1.5); potentiation of tilt-induced hypotension in the anesthetized rat showed substantial differences from the rabbit, with Rec 15/2739, but not Rec 15/3011 and Rec 15/2841 showing orthostatic effects equivalent to that observed for prazosin. Hence, Rec 15/2739 was uroselective in the rabbit, but not in the rat, while two of its close structural analogs were highly uroselective in both species. An assay for orthostatic activity in the conscious rat yielded different results, showing prazosin and terazosin, but not Rec 15/2739, to cause a reversal of the pressor response to tilt. Hence, the apparent uroselectivity of an α_1-adrenoceptor antagonist is both species- and assay-dependent.

Keywords: Benign prostatic hyperplasia; Orthostatic hypotension; Urethral perfusion pressure; Diastolic blood pressure

1. Introduction

In recent years, α_1-adrenoceptor antagonists have become widely used for the pharmacotherapy of benign prostatic hyperplasia. Although drugs such as alfuzosin, terazosin and doxazosin have shown convincing efficacy in large-scale placebo-controlled trials (Eri and Tveter, 1995; Lepor et al., 1996, 1997) and have become accepted in clinical practice, side-effects attributable to blockade of vascular α_1-adrenoceptors are observed in a significant percentage of treated patients. These side-effects include dizziness, asthenia, orthostatic hypotension and occasionally syncope. To reduce the incidence of vascular side-effects, therapy of prostatic hyperplasia with most α_1-adrenoceptor antagonists is initiated at a sub-therapeutic dose, followed by dose-titration until improvement of symptoms is attained.

To improve on current therapy, there has been widespread interest in the design of 'uroselective' α_1-adrenoceptor antagonists for the treatment of benign prostatic hyperplasia, i.e., antagonists which are able to block the α_1 adrenoceptors of the lower urinary tract without influencing vascular α_1 adrenoceptors. This effort has focused both on selectivity between α_1-adrenoceptor subtypes (Forray et al., 1994; Gluchowski et al., 1995; Buckner et al., 1997) and functional selectivity between vascu-

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lar and urethral responses in animal models (Testa et al., 1994; George et al., 1995; Blue et al., 1996; Kenny et al., 1994, 1996). Highly uroselective α_1-adrenoceptor antagonists have been identified using these animal models (Hieble and Ruffolo, 1996, 1997; Leonardi et al., 1996; Kenny et al., 1997); clinical evaluation of several of these compounds is currently ongoing.

We have demonstrated that Rec 15/2739 (*N*-[3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl]-3-methyl-4-oxo-2-phenyl-4*H*-1-benzopyran-8-carboxamide, also referred to in some reports as SB 216469) shows substantial uroselectivity in the anesthetized dog (Testa et al., 1994, 1997; Leonardi et al., 1996, 1997) with a 20–100-fold lower dose being required to block urethral contraction induced by exogenous α-adrenoceptor agonists or hypogastric nerve stimulation than that required to reduce basal diastolic blood pressure by 20%. This uroselectivity may result, in part, from the moderate selectivity of Rec 15/2739 for α_{1A} vs. α_{1B} and α_{1D} adrenoceptors (Testa et al., 1995), but is more likely to be related to its affinity for the putative α_{1L}-adrenoceptor. This premise is supported by the correlation of in vivo potency against norepinephrine-induced contraction with potency in an in vitro 'α_{1L}' model such as rabbit urethra or chloroethylclonidine-treated rabbit aorta for a diverse series of α_1 adrenoceptor antagonists. A correlation is not observed between in vivo potency at the dog urethra and affinity for the human recombinant α_{1a} adrenoceptor, especially for antagonists such as RS 17053 and SNAP 5089 which show high affinity for the α_{1a} adrenoceptor, but low affinity in 'α_{1L}' models (Hieble et al., 1996; Testa et al., 1996a, 1997; Leonardi et al., 1997). Comparison of the potency of Rec 15/2739 in canine prostate ('α_{1L}') with rat vas deferens (α_{1A}), shows a 5-fold higher potency at α_{1L}-adrenoceptors, compared to the 10–100-fold lower potency observed for prazosin or RS 17053 (Hieble and Ruffolo, 1997). Rec 15/2739 and several of its structural analogs have been shown to have high affinity for the α_1-adrenoceptor of human prostate (Testa et al., 1996b). Several other reports have confirmed the uroselectivity of Rec 15/2739 in the dog, comparing its ability to block urethral and vascular responsiveness to α-adrenoceptor activation (Blue et al., 1996; Brune et al., 1996; Kenny et al., 1996).

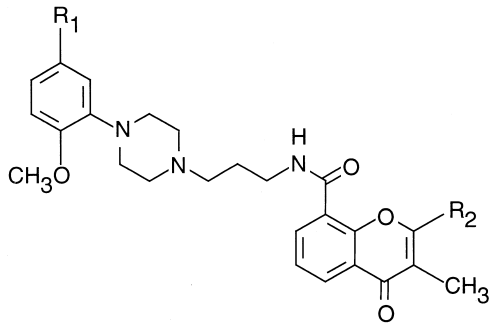
Since some of the vascular side-effects associated with α_1-adrenoceptor antagonist therapy of benign prostatic hyperplasia are induced or exacerbated upon standing, it may be appropriate to evaluate uroselectivity in animal models of orthostatic hypotension. In this report, we have determined the ability of Rec 15/2739, some close structural analogs, and other α_1-adrenoceptor antagonists to block urethral and vascular α_1-adrenoceptors in the rat and rabbit, and compared urethral blocking doses with those required to influence the blood pressure response to tilt in these species. This comparison may provide another index to predict whether these antagonists will be useful for blocking urogenital α_1-adrenoceptors in patients with prostatic hyperplasia without affecting the vascular response to assuming an erect posture.

2. Methods

2.1. Measurement of intraurethral perfusion pressure and blood pressure in rats and rabbits

Male Sprague–Dawley Rats or New Zealand White Rabbits were used for these experiments. In experiments using rabbits (1.6–3.0 kg body weight), anesthesia was induced by spontaneous ventilation with isoflurane (5% in O_2) delivered by means of an open circuit face mask at 1 l min^{-1}. When anesthesia was achieved, the isoflurane concentration was reduced to 2–3% in O_2 for the remainder of the experiment. For studies performed in the pithed rat, male rats (340–500 g body weight) were anesthetized with sodium methohexital (10 mg kg^{-1}, i.v.). The trachea was then rapidly cannulated and a pithing rod was inserted into the spinal canal via the orbit. Immediately after pithing, the rats were ventilated artificially (Harvard model 683; 60 strokes/min and 1 ml/100 g of body weight) with 100% O_2. Both rats and rabbits were kept warm by placing them on a heating pad (40°C). The left femoral vein and artery were cannulated with polyethylene tubing (Rat: 0.9 mm o.d., 0.58 mm i.d.; Rabbit: 1.3 mm o.d., 0.86 mm i.d.) for intravenous administration of drug and continuous monitoring of arterial blood pressure, respectively.

A midline suprapubic incision was made and the bladder and prostatic portion of the urethra were exposed. The bladder was manually emptied with a syringe. An inflow cannula (0.58 mm i.d., 0.96 mm o.d. for rats; 1.14 mm i.d., 1.57 mm o.d. for rabbits) was inserted through the dome of the urinary bladder and carefully secured with a ligature below the bladder neck, adjacent to the ureterodetrusor junction. A similar cannula was inserted into the penile urethra and advanced to the urethral bulb; this outflow cannula prevents resistive elements in the distal urethra from contributing to the proximal urethral perfusion pressure. The incision was closed in layers and the external inflow cannula was perfused (100 μl min^{-1} for rats and 200 μl min^{-1} for rabbits; Rainin Instrument Minipulse 2 peristaltic pump) with warm saline (37°C). Blood pressure and urethral perfusion pressure were recorded from the femoral artery and proximal urethra, respectively, by means of an electromechanical pressure transducer (Statham model P23 GB) and displayed on a polygraph (Grass model 7D). After a 15–30-min post-surgical stabilization period, an initial dose–response curve to phenylephrine was performed in either pithed rat or anesthetized rabbit to determine the reactivity of the preparation. When the blood pressure and urethral perfusion pressure returned to baseline, the animals were treated with vehicle (sterile water),



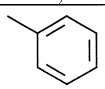
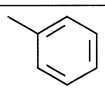
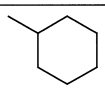
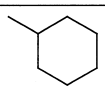
COMPOUND	R_1	R_2
Rec 15/2739	H	
Rec 15/2869	Cl	
Rec 15/2841	H	
Rec 15/3011	Cl	

Fig. 1. Structural formulae of Rec 15/2739 and analogs.

or α_1-adrenoceptor antagonist (slow i.v. bolus administration). Five minutes following this dosing, the concentration–response curve to phenylephrine was repeated. All changes in blood pressure and urethral perfusion pressure following drug treatment were compared to vehicle-treated group.

2.2. Orthostatic hypotension models

2.2.1. Sedated hypovolemic rabbits

New Zealand White rabbits (1.5–2.2 kg body weight) were anesthetized with sodium methohexital (< 30 mg kg^{-1}, i.v.). The left femoral vein and carotid artery were cannulated with polyethylene tubing (1.22 mm o.d., 0.76 mm i.d.). Intravenous administration of drug was via the marginal ear vein (26 g, 1.5 in. needle). Blood pressure was monitored via arterial cannula by means of a pressure transducer (Statham model P23 GB) which was secured on the tilt box at the level of the heart and displayed on a polygraph (Grass model 7D). A generous amount of a 5% Lidocaine ointment was applied to the incision area of the neck muscle fascia before the dermal opening was closed with 9-mm wound clips, and the rabbit was returned to the box, where it was permitted at least a 30-min recovery period. The entire surgical procedure lasted approximately 15–20 min and required no more than 30 mg kg^{-1} of intravenous methohexital. Rabbits were bled (5 ml kg^{-1}) from the cannulated carotid artery, and then supplemented with a low dose of sodium pentobarbital (15 mg kg^{-1}, i.v.), via the femoral venous cannula, prior to the administration of drugs via the marginal ear vein. Preliminary experiments showed this bleeding and barbiturate supplement to have no effect on basal blood pressure or the control response to tilt; however, this did increase consistency of the orthostatic effect seen upon administration of prazosin. At least two control responses to 90° tilt were performed, prior to drug administration. Animals remained tilted in the vertical position for a period of 60 s and changes in diastolic blood pressure were recorded at 10-s

Table 1
Blockade of the phenylephrine-induced increases in urethral perfusion pressure and diastolic blood pressure in the anesthetized rabbit

Treatment	Dose ($\mu g\ kg^{-1}$, i.v.)	$UPPD_6$ (mean ratio ± S.E.M.)[a]	$DBPD_{40}$ (mean ratio ± S.E.M.)[b]
Rec 15/2739	10	6.8 ± 1.5	1.8 ± 0.2
	100	73 ± 16	11 ± 2.4
Rec 15/3011	10	4.3 ± 0.9	2.9 ± 0.2
	20	27 ± 15	12 ± 4
	50	65 ± 35	23 ± 7
Rec 15/2841	50	39 ± 15	26 ± 4.6
Rec 15/2869	100	44 ± 9	9.6 ± 3.8
Alfuzosin	300	9.2 ± 1.1	8.2 ± 2.1
Doxazosin	300	6.9 ± 2.2	6.8 ± 0.8
Prazosin	100	7.6 ± 2.2	8.4 ± 1.5
Terazosin	300	41 ± 15	45 ± 28
SL 89.0591	100	18 ± 3	9 ± 1
Tamsulosin	10	51 ± 4	21 ± 4
Vehicle		1.5 ± 0.2	1.5 ± 0.4

[a] $UPPD_6$ treatment/$UPPD_6$ vehicle. $UPPD_6$ is defined as the dose of phenylephrine required to increase urethral perfusion pressure by 6 mmHg.
[b] $DBPD_{40}$ treatment/$DBPD_{40}$ vehicle. $DBPD_{40}$ is defined as the dose of phenylephrine required to increase diastolic blood pressure by 40 mmHg.
Values represent the means of at least four experiments.

intervals during the tilt. Drugs were administered via i.v. infusion using an infusion pump which delivered a volume of 100 μl min^{-1}. Liability of these drugs for production of orthostatic hypotension was tested during the fourth to fifth minute of a 5-min i.v. infusion.

2.2.2. Anesthetized rats

Male Sprague–Dawley rats (250–300 g body weight) were anesthetized with sodium pentobarbital (35 mg kg^{-1}, i.v.). During surgery, animals were kept warm by placing them on a water-circulating heating pad maintained at 40°C. The left femoral vein and carotid artery were cannulated with polyethylene tubing (0.9 mm o.d., 0.58 mm i.d.). Intravenous administration of drug was via a surgically implanted polyethylene tube (0.9 mm o.d., 0.58 mm i.d.). Blood pressure was monitored via the arterial cannula by means of a pressure transducer (Statham model P23 GB) which was secured on a tilt table at the level of the heart and displayed on a polygraph (Grass model 7D). Blood pressure stabilized in about 5 min following antago-

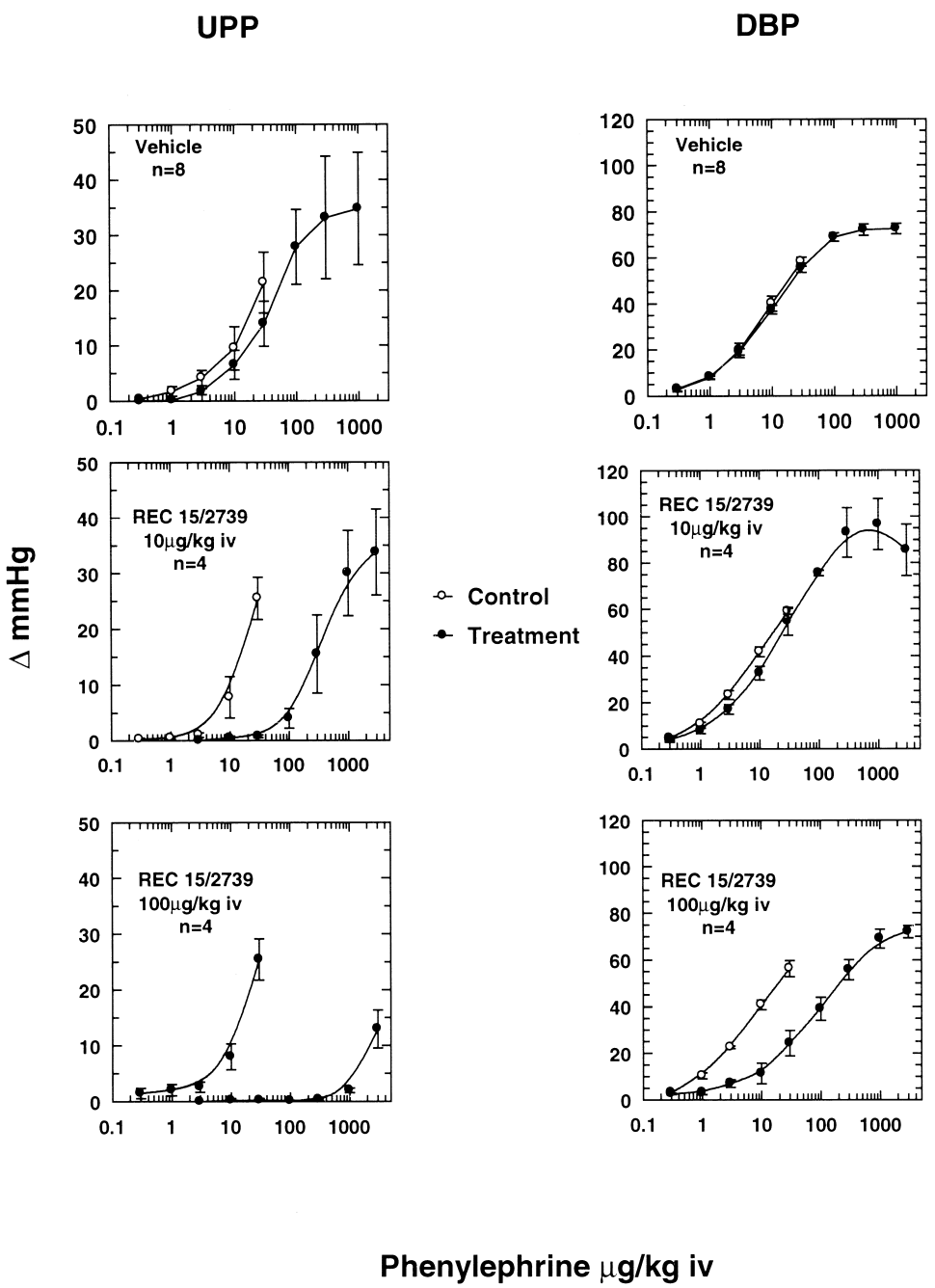


Fig. 2. Effect of phenylephrine on diastolic blood pressure (DBP) and urethral perfusion pressure (UPP) in anesthetized rabbit and blockade of this action by Rec 15/2739. Values represent mean ± S.E.M.

nist administration. At least two control responses to 90° head-up tilt were performed, prior to drug administration. Animals remained tilted in the vertical position for a period of 60 s and changes in diastolic blood pressure were recorded at 10-s intervals during the tilt. Drugs were administered via i.v. infusion using an infusion pump which delivered a volume of 100 μl min^{-1}. Liability of these drugs for production of orthostatic hypotension was tested during the fourth to fifth minute of a 5-min i.v. infusion.

2.2.3. Conscious rats

Under surgical anesthesia (Halothane/Nitrous Oxide), the left carotid artery and left jugular vein were cannulated, and the cannulae exteriorized at the back of the neck. Following at least 24 h recovery from surgery, the rats were placed in plastic tubes mounted on pivots. Arterial cannulae were connected to a pressure transducer to allow continuous blood pressure measurement. Rats were tilted heads up for 15 s by rotating the plastic tube 90°. Tilting was repeated at 5-min intervals for 30 min to

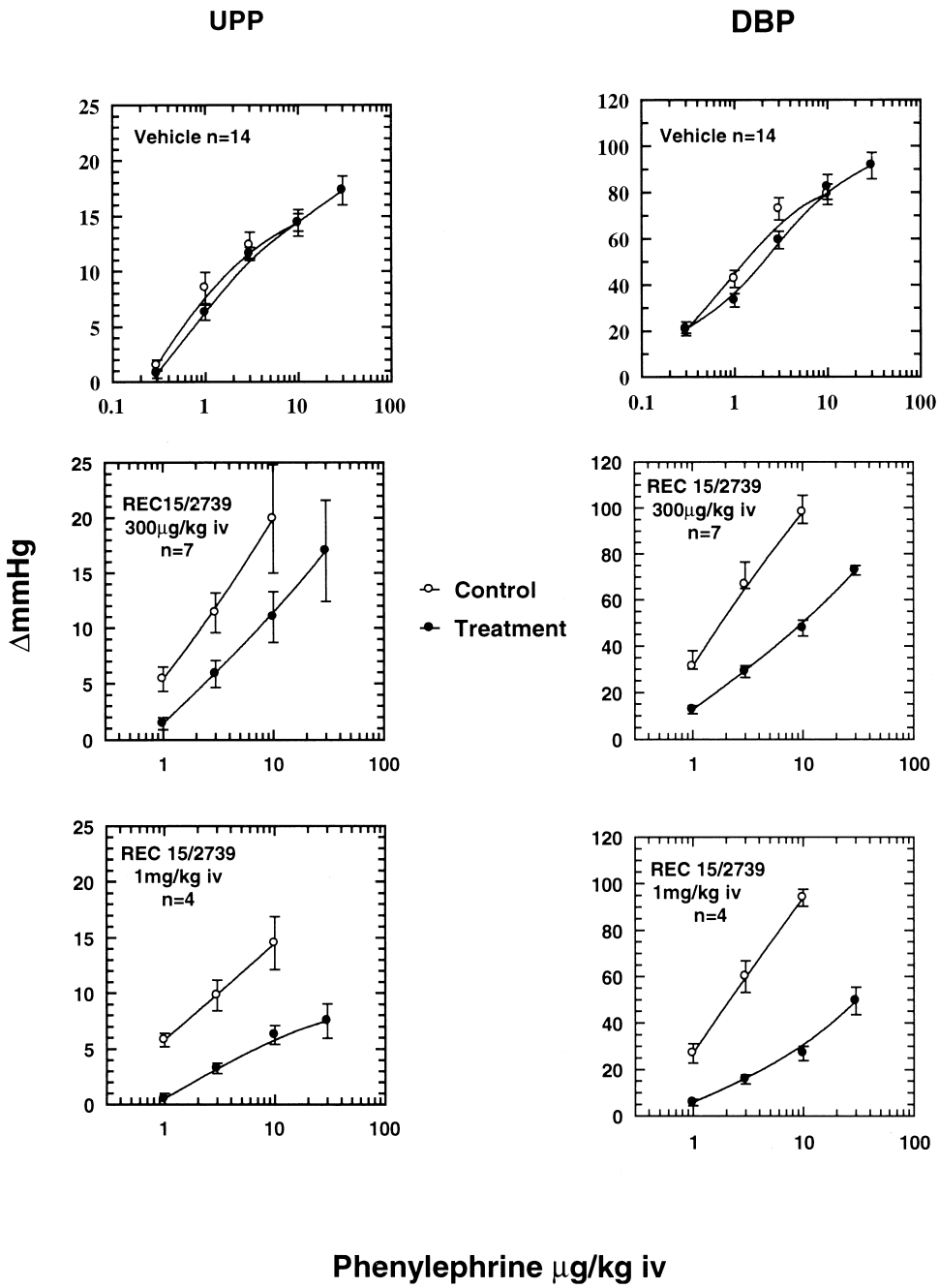


Fig. 3. Effect of phenylephrine on diastolic blood pressure (DBP) and urethral perfusion pressure (UPP) in the pithed rat and blockade of this action by Rec 15/2739. Values represent mean ± S.E.M.

acclimate the animals to the procedure. The orthostatic response was defined as the maximum increase in blood pressure observed during the 15-s tilt. A mean of the values from the final two tilts prior to drug administration was taken as the pre-dose value. Vehicle or drug was administered in cumulatively increasing doses at 15-min intervals through the venous cannula. Tilt was repeated 15 min after each drug administration.

2.3. Statistical analysis

The dose of phenylephrine that increased diastolic blood pressure by 40 mmHg (or the urethral pressure by 6 mmHg was calculated from log dose–response curves for each treated group using regression analysis. These doses were compared for each animal before and after drug administration. First and second dose–response curves to phenylephrine in vehicle-treated animals were nearly identical for all responses, with a shift to the right of 2-fold or less in all cases (Figs. 2 and 3). The magnitude of the orthostatic effect was expressed as the area under the time vs. diastolic blood pressure curve.

2.4. Drugs

Drugs were dissolved in sterile water except phenylephrine which was dissolved in saline. The chemical structures of Rec 15/2739 and its structural analogs are shown in Fig. 1; these compounds, as well as tamsulosin and SL 89.0591, were synthesized at Recordati Research Department, Milan, Italy. Alfuzosin was generously provided by Synthelabo (Paris) and doxazosin by Pfizer USA (Groton, CT). Terazosin was synthesized by the Medicinal Chemistry Department of SmithKline Beecham Pharmaceuticals. Prazosin was obtained from Sigma, St. Louis, MO. (−)Phenylephrine hydrochloride was obtained from Sterling Organics, Rensselaer, NY.

3. Results

3.1. Phenylephrine challenge

Experiments in the anesthetized rabbit and pithed rat showed all of the α_1-adrenoceptor antagonists to produce blockade of both the increase in urethral perfusion pressure and increase in diastolic blood pressure produced by phenylephrine. This effect was quantitated by evaluating the ratios between the doses of phenylephrine inducing an increase of 6 and 40 mmHg in urethral perfusion pressure and diastolic blood pressure, respectively, before and after treatment with the antagonists (Table 1). 40 mmHg represented nearly a half-maximal response in blood pressure in both the rabbit (Fig. 2) and rat (Fig. 3) models. 6 mmHg was substantially less than the half-maximal response in urethral perfusion pressure, especially in the rabbit. This level was, however, chosen to allow quantitation of the urethral response in the presence of higher antagonist doses, where maximum responses of only about 10 mmHg could be attained at phenylephrine doses tolerated by the animal.

3.1.1. Rabbit

Multiple doses of Rec 15/2739 and Rec 15/3011 were evaluated, and the magnitude of the blockade was dose-related. Rec 15/2739, Rec 15/2869 and Rec 15/3011 all showed uroselectivity in this model, producing a 2–6-fold greater shift in the urethral response. Tamsulosin and SL 89.0591 also showed moderate uroselectivity. Rec 15/2841 showed only a slight degree of uroselectivity, while the quinazolines (prazosin, doxazosin, terazosin and alfuzosin) were equipotent against urethral and vascular responses.

3.1.2. Rat

Comparison of the potencies of α_1-adrenoceptor antagonists against phenylephrine-induced increases in urethral perfusion pressure and diastolic blood pressure in the pithed rat showed a different pattern than observed in the anesthetized rabbit. With the exception of the 300 mg kg^{-1} dose of terazosin, none of the antagonists was uroselective, most compounds showing equivalent potency against urethral and vascular responses. Tamsulosin showed selectivity for the vascular response at both doses tested (Table 2). Interestingly, while terazosin and prazosin have approximately equal potency at urethral α_1-adrenoceptors in the two species, the other antagonists are from 10–50-fold less potent in the rat.

Table 2
Blockade of the phenylephrine-induced increases in urethral perfusion pressure and diastolic blood pressure in the pithed rat

Compound	Dose ($\mu g\ kg^{-1}$, i.v.)	$UPPD_6$ ratio[a]	$DBPD_{40}$ ratio[b]
Rec 15/2739	300	3.4	3.7
	1000	8.6	13.4
Rec 15/3011	300	4.4	4.4
	1000	18.4	12
SL 89.0591	100	4.5	5.8
	300	5.6	4.8
	1000	9.5	6.8
Rec 15/2841	100	3.7	5.8
Prazosin	30	3.7	20.1
	100	34.1	> 30
Tamsulosin	3	1.7	17.7
	10	4.6	17.0
Terazosin	100	2.6	5.8
	300	30	4.8
Vehicle		1.5	2.1

[a] $UPPD_6$ treatment/$UPPD_6$ vehicle.
[b] $DBPD_{40}$ treatment/$DBPD_{40}$ vehicle.

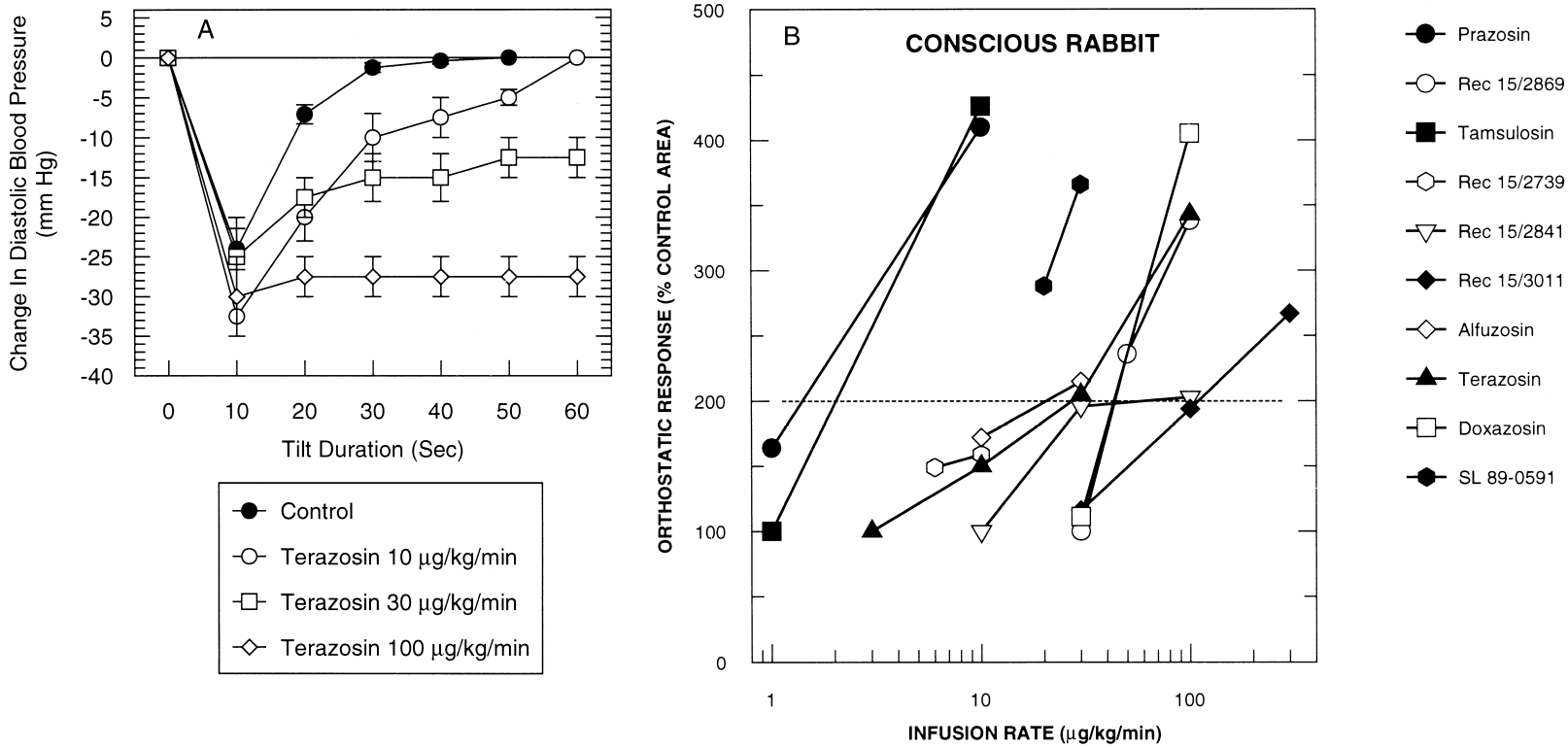


Fig. 4. (A) Effect of increasing infusion rates of terazosin on the diastolic blood pressure response to a 60-s, 90°, head-up tilt in the sedated hypovolemic rabbit. Rabbits were bled (5 ml/kg) from the carotid artery, and sedated with sodium pentobarbital (15 mg/kg, i.v.), 5 min prior to initiation of drug infusion. The area enclosed by the time vs. response curves and the *X* axis was calculated. Drugs were infused for 5 min, and tilt was initiated after 4 min of infusion. Each curve represents the mean of 12 (control) or three experiments (terazosin doses) ± S.E.M. (B) Relationship between infusion rate and area under the blood pressure vs. time curve during a 60-s tilt in the sedated hypovolemic rabbit. Area under the curve calculated from mean time vs. diastolic pressure curves such as those shown in panel A. Infusion rate required to double this area was used to quantitate orthostatic liability.

3.2. Orthostatic hypotension assays

3.2.1. Sedated hypovolemic rabbit

We have previously shown that α-adrenoceptor antagonists will potentiate the hypotensive response to tilt in the conscious hypovolemic rabbit (Hieble et al., 1985). In this experimental series, we found that the consistency of the data was improved if the rabbits were sedated with intravenous pentobarbital prior to initiation of antagonist infusion. Fig. 4 shows the effect of α_1-adrenoceptor antagonist administration on the hypotensive response to tilt in this rabbit model, as quantitated by area under the diastolic blood pressure vs. time curve during the 1-min tilt (Fig. 4A). Most of the antagonists produced a dose-related potentiation of the orthostatic response, although in many cases, only a limited range of doses could be studied. Higher doses than those shown in Fig. 4B were tested for several antagonists. These doses had less of an effect on area under the curve (data not shown), probably due to reduction of pre-tilt blood pressure (Table 3) which consequently limits the further reduction which can be produced in response to tilt.

Most of the antagonists could produce a 3.5–4-fold potentiation of the orthostatic response (Fig. 4B). However, Rec 15/2739, Rec 15/2841 and Rec 15/3011 produced a lower maximum response (1.5–2.5-fold increase). The doses of Rec 15/3011 required to produce an orthostatic response in this model were particularly high, in relation to the potency of this compound against the urethral response to phenylephrine in the anesthetized rabbit (Table 1).

3.2.2. Anesthetized rat

Fig. 5 compares the ability of the α_1-adrenoceptor antagonists to potentiate tilt-induced hypotension in the anesthetized rat. For all antagonists, reductions in pre-tilt blood pressure (Table 4) were generally less pronounced than those observed in the rabbit (Table 3). As observed in the rabbit, prazosin and tamsulosin were the most potent agents in this model. However, in contrast to the results obtained in the rabbit, Rec 15/2739 produced a maximum effect on the orthostatic response comparable to that of prazosin and tamsulosin, at low doses relative to its potency at urethral α_1-adrenoceptors (Table 3). Interestingly, although Rec 15/2841 and Rec 15/3011 did not show uroselectivity in the rat, as evaluated by comparison of their potency against the urethral and blood pressure responses to phenylephrine (Table 3), they were substantially less potent than Rec 15/2739 in potentiating tilt-induced hypotension, and produced a lower maximum response (Fig. 5).

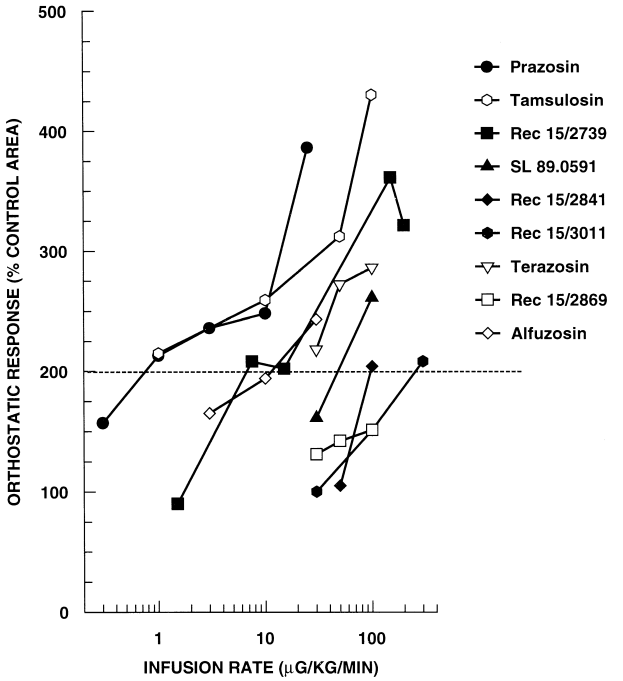


Fig. 5. Effect of α_1-adrenoceptor antagonists on the blood pressure response to a 60-s, 90°, head-up tilt in the anesthetized rat. Response expressed as a percentage change in the area under the blood pressure vs. time curve during the 60-s tilt (see Fig. 4A). Drugs were infused for 5 min, and tilt was initiated after 4 min of infusion.

Table 3
Effect (absolute reduction in mmHg ± S.E.M.) of α_1-adrenoceptor antagonist infusion on pre-tilt diastolic blood pressure in the sedated hypovolemic rabbit

Compound	Antagonist infusion rate (μg kg^{-1} min^{-1})								
	1	3	6	10	20	30	50	100	300
Prazosin	5 ± 2			10 ± 3	15 ± 4				
Tamsulosin	0			23 ± 4		35 ± 8			
Rec 15/2739			0	6.7 ± 1.4		17 ± 2		28 ± 2	
SL 89.0591	0			5 ± 1	15 ± 3	25 ± 5			
Alfuzosin				5 ± 2		15 ± 3		28 ± 1.4	33 ± 2
Terazosin		0		8 ± 2		15 ± 2		28 ± 2	
Doxazosin				2 ± 2		4 ± 2		25 ± 4	
Rec 15/2869						3 ± 3	10 ± 2	8 ± 1.4	
Rec 15/2841	0			10 ± 5		14 ± 2		28 ± 8	
Rec 15/3011						0		15 ± 2	30 ± 4

Values represent the means of at least four experiments.

Table 4
Effect (absolute reduction in mmHg ± S.E.M.) of α_1-adrenoceptor antagonist infusion on pre-tilt diastolic blood pressure in the anesthetized rat

Compound	Antagonist infusion rate ($\mu g\ kg^{-1}\ min^{-1}$)								
	1	3	7.5	10	25	30	50	100	300
Prazosin	0	5 ± 2.4		10 ± 3	16 ± 3				
Tamsulosin	6.3 ± 1.1			7.5 ± 1.3				20 ± 2.4	
Rec 15/2739	0		11 ± 3					9.0 ± 1.7[a]	8.3 ± 1.4[b]
SL 89.0591								8.3 ± 1.4	
Alfuzosin		5 ± 1.8		10 ± 3		15 ± 4		17 ± 3	
Terazosin	0			6.3 ± 2.1		10 ± 2	13 ± 2		27 ± 1.4
Doxazosin							10		
Rec 15/2869						0	0	8 ± 1.5	
Rec 15/2841								11 ± 2	
Rec 15/3011								5 ± 1	3.3 ± 1.4

[a]150 $\mu g\ kg^{-1}\ min^{-1}$.
[b]200 $\mu g\ kg^{-1}\ min^{-1}$.
Values represent the means of at least four experiments.

3.2.3. Conscious rat

Orthostatic liability can also be evaluated in the conscious rat, measuring the effect of i.v. bolus administration of the antagonists on the pressor response to upright tilt. In this model, both prazosin and terazosin produced a reversal of this response, so that after drug administration, tilt reduced blood pressure (Fig. 6). The doses of the quinazolines required to produce this response were equal. In contrast to the equivalent or greater orthostatic liability of Rec 15/2739 vs. prazosin and terazosin in the anesthetized rat (Fig. 5), even very high intravenous doses of Rec 15/2739 failed to reverse the tilt-induced pressor response in the conscious rat, and doses up to 300 $\mu g\ kg^{-1}$ produced no significant reduction in the magnitude of this response.

4. Discussion

Studies in dogs have consistently demonstrated that Rec 15/2739 blocks urethral α_1-adrenoceptors at doses substantially lower than required to block vascular α_1-adren-

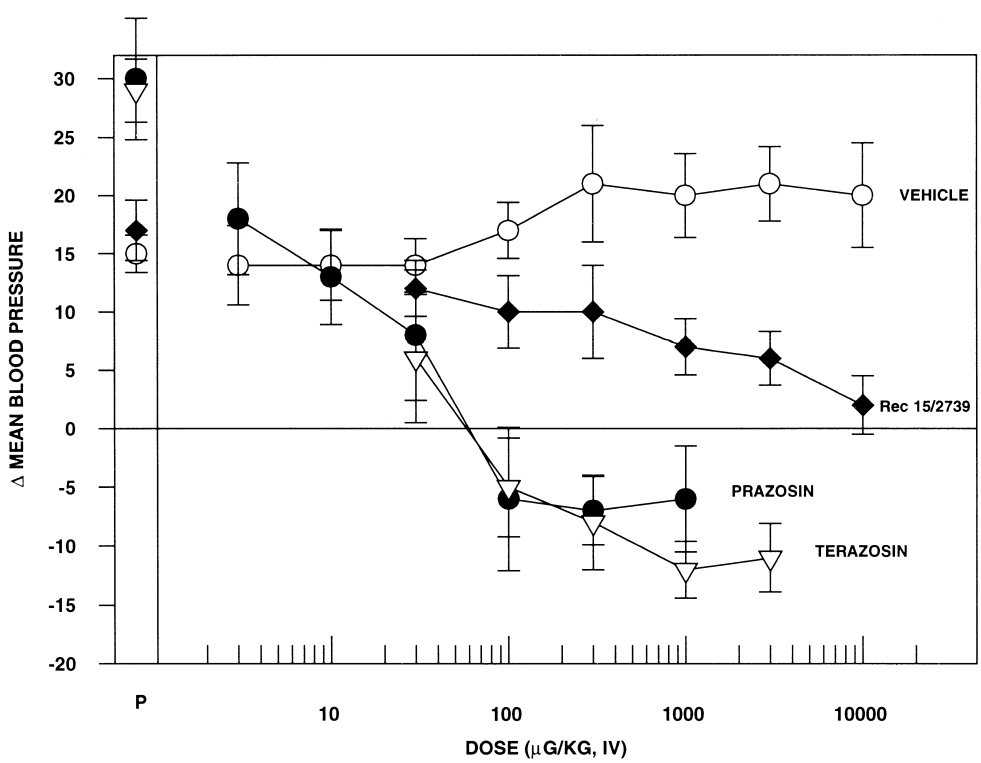


Fig. 6. Effects of prazosin, terazosin and Rec 15/2739 on the blood pressure response to tilt in the conscious rat. Symbols to far left (P) denote change in tilt-induced increases in blood pressure in the four groups prior to drug treatment. Each point represents the mean of eight animals ± S.E.M.

oceptors. This is demonstrated either by comparing antagonist potency against the increases in urethral perfusion pressure and diastolic blood pressure induced by an α_1-adrenoceptor agonist (Blue et al., 1996; Brune et al., 1996; Kenny et al., 1996), or by comparing blockade of the urethral α_1-adrenoceptor with reduction in basal diastolic blood pressure (Testa et al., 1994, 1997; Leonardi et al., 1997). In the latter model, Rec 15/2739 shows a 101-fold dose ratio; its structural analogs, Rec 15/2841, Rec 15/2869 and Rec 15/3011, show equivalent uroselectivity, with dose ratios ranging from 54 to 112 (Testa et al., 1997).

Prazosin, terazosin and doxazosin generally block urethral and vascular responses in the dog at equivalent or nearly equivalent doses, regardless of the model employed (Kenny et al., 1994, 1996; Blue et al., 1996; Brune et al., 1996; Testa et al., 1997). Alfuzosin shows a modest degree of uroselectivity when urethral blockade is compared to reduction in diastolic blood pressure (dose ratio = 7) (Testa et al., 1997). Studies in the rat, measuring direct effects on basal urethral and blood pressures, have shown alfuzosin to show uroselectivity (Martin et al., 1997). The magnitude of the uroselectivity observed by Testa et al. (1997) for tamsulosin in the dog is comparable to that observed for alfuzosin (dose ratio = 10). In other anesthetized dog models, tamsulosin shows no uroselectivity (Kenny et al., 1994; Blue et al., 1997), while modest uroselectivity is observed in the conscious dog (Brune et al., 1996). SL 89.0591 has been reported to have substantially greater uroselectivity than alfuzosin, terazosin or prazosin, comparing urethral blocking doses in the anesthetized cat with those required to reduce blood pressure in the spontaneously hypertensive rat (George et al., 1995). This is consistent with the observation that, in the anesthetized dog, SL 89.0591 shows uroselectivity intermediate between tamsulosin and Rec 15/2739 (Blue et al., 1996; Testa, unpublished data).

Determination of the uroselectivity of these antagonists in the anesthetized rabbit yielded results in reasonable agreement with the above observations in the dog. As shown in Table 1, in anesthetized animals, Rec 15/2739 was 4–6.5-fold more potent against the urethral vis-a-vis the vascular response to phenylephrine. Its structural analogs, Rec 15/2869 and Rec 15/3011, showed comparable uroselectivity in this model, while Rec 15/2841 appeared less uroselective. Comparison of selectivity ratios for Rec 15/2841 (54) and Rec 15/2739 (101) in the dog (Testa et al., 1997) suggest that Rec 15/2841 might be somewhat less uroselective. Also consistent with the data in the dog, tamsulosin, SL 89.0591 showed about 2-fold greater potency against the urethral response to phenylephrine in the rabbit, while the quinazolines were virtually equipotent against the urethral and vascular responses (Table 1).

While terazosin was equipotent to prazosin as an antagonist of urethral α_1-adrenoceptors in the anesthetized rabbit (Table 1), much higher terazosin doses were required to potentiate the orthostatic response in the sedated hypovolemic rabbit (Fig. 4B); likewise, while doxazosin and alfuzosin were about 3-fold weaker than prazosin as α_1-adrenoceptor antagonists in the anesthetized rabbit, they were at least 30-fold weaker in the rabbit orthostatic hypotension model (Fig. 4B). When these antagonists are used clinically for the symptomatic treatment of BPH symptoms, it also appears that the more recently developed quinazolines are associated with a lower incidence of syncope, dizziness and orthostatic hypotension than prazosin, although this may be attributable, at least for terazosin and doxazosin, to differences in pharmacokinetic profile. While tamsulosin has equivalent orthostatic potency to prazosin (Fig. 4B), it is much more potent as a urethral α_1-adrenoceptor antagonist in the anesthetized rabbit (Table 1). Tamsulosin, administered clinically as a delayed release preparation without dose titration, does not either reduce basal blood pressure or produce orthostatic hypotension (Schulman et al., 1996; Beduschi et al., 1998; Lepor, 1998a,b). A significantly greater incidence of dizziness and/or asthenia compared to placebo is observed in some studies (Schulman et al., 1996; Lepor, 1998a), although the clinical impression is that tamsulosin has less 'vascular-related' side-effects than the quinazoline α_1-adrenoceptor antagonists (Lee and Lee, 1997; Beduschi et al., 1998). Rec 15/2739, Rec 15/2841, Rec 15/2869 and Rec 15/3011 all are more potent than prazosin as urethral α_1-adrenoceptor antagonists in the anesthetized rabbit (Table 1); however, in the orthostatic hypotension model, all of these compounds are much less potent (Fig. 4B). If one compares urethral α_1-adrenoceptor antagonist potency with orthostatic liability, these data show Rec 15/3011 to differ from prazosin by about 1000-fold (10-fold more potent as an α_1-adrenoceptor antagonist, 100-fold less potent in inducing orthostatic hypotension).

Comparing uroselectivity as determined in these two rabbit models suggests the contribution of an additional factor, as yet uncharacterized, to the ability to potentiate tilt-induced hypotension, in addition to the relative ability to block urethral and vascular α_1-adrenoceptors. The antagonists showing uroselectivity against the responses to phenylephrine in the anesthetized rabbit show, in relation to their urethral α_1-adrenoceptor antagonist potency, less orthostatic liability than those having equivalent potency against urethral and vascular responses. However, in both the uroselective and non-uroselective groups, there are substantial differences in relative orthostatic liability between individual antagonists which cannot be attributed to differences in potency against the urethral and vascular responses to phenylephrine.

None of the antagonists tested showed consistent uroselectivity as measured by potency against the urethral and vascular responses in the pithed rat (Table 2). Prazosin and terazosin had equivalent potency at urethral α_1-adrenoceptors in rat and rabbit; in contrast, the potency of several of

the other antagonists, particularly Rec 15/2739 and its analogs, was much lower in the rat (compare Tables 1 and 2). This may be a consequence of a contribution of the α_{1L}-adrenoceptor to the urethral response to phenylephrine in the rabbit, but not in the rat. It has been shown that Rec 15/2739 and its analogs interact with α_{1L}-adrenoceptors in isolated rabbit urethra or bladder neck (Leonardi et al., 1997; Testa et al., 1997; Kava et al., 1998), while the α_1-adrenoceptor subtype responsible for urethral contraction in the rat has not been characterized; α_{1L}-adrenoceptors have not been convincingly demonstrated in this species.

As observed in the rabbit model, terazosin showed less orthostatic liability than prazosin in the anesthetized rat, and both Rec 15/2841 and Rec 15/3011 showed much less orthostatic liability than Rec 15/2739 (Fig. 5). These results are similar to those observed in the rabbit, and are consistent with the premise that another factor, in addition to differential blockade of urethral and vascular α_1 adrenoceptors, contributes to orthostatic liability.

Rec 15/2739 showed orthostatic liability equivalent to that of prazosin in the anesthetized rat, if its low potency against urethral α_1-adrenoceptors in this species is considered. In contrast, studies in the conscious rat show that, unlike prazosin and terazosin, Rec 15/2739 does not convert the tilt-induced pressor response to a fall in blood pressure, even at very high doses (Fig. 6). This suggests a difference in the mechanisms controlling vascular tone in conscious and anesthetized rats and a qualitative difference, at least in conscious animals, between Rec 15/2739 and the quinazolines.

It is clear that the apparent uroselectivity of an α_1-adrenoceptor antagonist can be highly dependent on the experimental model used to evaluate affinity at prostate/urethral and vascular sites. While comparison of the ability to block a urethral and vascular response to α_1-adrenoceptor activation may provide the most direct comparison of affinities at these receptors, the uroselectivity determined by this assay may not be predictive of selectivity in models measuring a less direct, but perhaps more clinically relevant, consequence of vascular α_1-adrenoceptor blockade, such as the blood pressure response to tilt. It is not known which, if any, of these models will be predictive of clinical uroselectivity. Nevertheless, the observation that compounds such as Rec 15/2841, Rec 15/2869 and Rec 15/3011 have the lowest orthostatic liability, relative to potency at urethral α_1-adrenoceptors, regardless of species, shows a potential advantage over α_1-adrenoceptor antagonists currently available for the treatment of benign prostatic hyperplasia.

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