The human prostatic smooth muscle contains high densities of alpha-1-adrenoceptors (Muramatsu et al., 1994; Hieble et al., 1985; James et al., 1989) and several alpha-1-adrenoceptor subtypes have been identified and their heterogeneity revealed both pharmacologically and by molecular cloning (Michel et al., 1993; Price et al., 1993). The three alpha-1-adrenoceptor subtypes with high affinity for prazosin, so far identified, i.e., alpha-1A, alpha-1B and alpha-1D-adrenoceptors, have been cloned (alpha-1a, alpha-1b and alpha-1d). The pharmacology of the cloned receptors has been characterized against that of their native forms (Michel and Insel, 1994; Blue et al., 1995). The alpha-1a-adrenoceptor subtype has been described to be predominant in the human prostate, either using molecular biology techniques (Price et al., 1993; Faure et al., 1994; Forray et al., 1994) or autoradiography (Kobayashi et al., 1993). However, whether this adrenoceptor subtype plays a prevalent role in mediating contractile responses of the prostatic tissue remains a controversial issue. Initial in vitro studies on the efficacy of various alpha-1-adrenoceptor antagonists at inhibiting noradrenaline or phenylephrine-mediated contraction suggested that contractile potency is well correlated with binding affinities for the alpha-1a subtype (Forray et al., 1994). Nevertheless, recent data using more selective alpha-1a-adrenoceptor antagonists suggest that the alpha-1a-adrenoceptor subtype that mediates prostatic contraction does not have all the pharmacological characteristics of the alpha-1A-adrenoceptor (Ford et al., 1996; Kenny et al., 1996, Van Der Graaf et al., 1996).

In recent years, attempts have been made to evaluate the selective effects of alpha-1-adrenoceptor antagonists on prostatic tissue compared to side effects, most particularly the effects on blood pressure. Only a limited number of in vivo methodologies are available to specifically evaluate the mechanisms that explain the preferential action of some alpha-1-adrenoceptor antagonists at the prostatic level (Kenny et al., 1994; Lefèvre-Borg et al., 1992, 1993) and all reported results appeared to depend on the species and experimental conditions. Use of exogenous stimulation or interspecies comparisons lead to difficulties in analyzing the respective action of the tested drugs on the vasculature and the functional uroselectivity of these antagonists based on their respective effects on both pressures. Dose ranges were selected according to effects on urethral pressure and most antagonists were found effective within the 3 to 100 μg/kg i.v. range. Prazosin markedly decreased urethral pressure and either did not decrease blood pressure (10–30 μg/kg) or slightly decreased it at the highest dose tested (100 μg/kg). Doxazosin did not produce sustained reductions in urethral pressure until a dose of 30 μg/kg. Blood pressure was not reduced until 100 μg/kg. Prazosin reduced urethral pressure and blood pressure within the same dose-range whereas terazosin did not decrease urethral pressure at doses that significantly decreased blood pressure (30 and 100 μg/kg). 5-Me-urapidil, an alpha-1a-selective compound did not significantly modify urethral and blood pressure whereas tamsulosin, another alpha-1a-selective compound reduced urethral pressure and blood pressure within the same dose range. In conclusion, in the conscious male rat the functional uroselectivity is not correlated with a selective affinity for the alpha-1a-adrenoceptor subtype.
on the urinary tract. We have recently developed a new model that allows the simultaneous measurement of urethral and arterial pressures in conscious male rats (Martin et al., 1995) therefore enabling a direct estimation of functional uroselectivity.

The theoretical value of alpha-1-adrenoceptor antagonists in the treatment of BPH is well established (Jonler et al., 1994; Eri et al., 1995) and recent development in the identification and distribution of alpha-1-adrenoceptors have revitalized the question of adrenoceptor subtype selectivity and functional uroselectivity of available drugs. Our study was undertaken to assess the functional uroselectivity of several alpha-1-adrenoceptor antagonists in the conscious male rat under normal adrenergic tone and to relate this uroselectivity with their affinities for the cloned alpha-1-adrenoceptor subtypes and with their efficacy to antagonize phenylephrine-induced contractions of prostatic tissue in vitro.

Methods

Receptor Binding Assays

Cell culture and membrane preparations. HeLa cell-lines stably expressing the bovine brain alpha1a-adrenoceptor, the hamster smooth muscle alpha1b-adrenoceptor and a rat fibroblast cell-line stably expressing the rat cerebral cortex alpha1d-adrenoceptor were purchased from Tulco (Durham, NC). Transfected cells were cultured in monolayers in Dulbecco modified medium with 4500 mg/liter glucose supplemented with 10% fetal calf serum, penicillin (50 U/ml), streptomycin (50 U/ml) and gentamicin (400 μg/ml). Cells were harvested in phosphate-buffered saline, collected and centrifuged at 140,000 g for 5 min. Subsequently, the cells were homogenized in 5 mM Tris-HCl buffer, pH 7.4, containing 5 mM EDTA and centrifuged at 46,000 g for 20 min. The pellets were resuspended in 50 mM Tris-HCl buffer, pH 7.4, recentrifuged, pooled in buffer and frozen at −80°C until binding studies.

Radioligands binding assays. Ligand binding studies were performed in 50 nM Tris-HCl buffer, pH 7.4. Cell membrane preparations (4 μg protein) were incubated with [3H] prazosin at 25°C for 1 hr in a total volume of 2 ml. Parameters of [3H] prazosin binding have been presented elsewhere (Faure et al., 1994). Phentolamine (10 μM) was used to define nonspecific binding. Incubations were terminated by rapid filtration using a Brandel Cell Harvester (Neurrolab, Paris, France) through Whatman GF/B glass fiber filters. The filters were washed with 2 × 5 ml of buffer, dried and the radioactivity was measured in a liquid scintillation counter.

The concentration of each drug that inhibited specific binding by 50% (IC50) was used to calculate Kᵢ values using the Cheng-Prusoff equation. The affinities of each drug have been expressed by the negative logarithms of their Kᵢ (pKi).

Rabbit Isolated Prostate Preparation

Male New Zealand rabbits (18 wk; ESD, Chatillon Sur Chalaroye, France) were killed by cervical dislocation and exsanguination and the prostate was removed and placed in modified Krebs-Laroyne, France) were killed by cervical dislocation and exsanguination. Tissue responses were measured continuously using Grass FT03 isometric transducers and displayed on a Grass 7D polygraph (Quincy, MA).

After application of 1 g resting tension, tissues were allowed to equilibrate for 90 min during which time the organ bath fluid was replaced regularly. Subsequently, tissues were exposed to two consecutive concentrations of noradrenaline (30 μM), separated by 60-min washout periods. After an additional 60-min washout period, a first E/A curve was constructed by cumulative additions as half-log unit concentration increments. Tissues were then washed for 60 min and incubated for 30 min with antagonist or vehicle before a second phenylephrine E/A curve was done. Only one concentration of antagonist was studied in each tissue. Propranolol (1 μM) was present in all experiments to block β-adrenoceptors.

Individual phenylephrine E/A curves were fitted to the Hill equation using the ALFfit program to provide estimates of midpoint location (EC50). Each pair of EC50 values obtained in the absence and presence of antagonist was then used to calculate the concentration ratio (EC50 in the presence of antagonist divided by the EC50 of the control curve) and antagonist dissociation equilibrium constants (Kd, represented as the negative logarithm, that is pKd) were calculated according to the method of Schild (Jenkinson, 1991).

In Vivo Methods

Simultaneous assessment of blood pressure and urethral pressure was undertaken as recently described (Martin et al., 1995). Briefly, male Wistar rats (350–400 g, Charles River, Saint Aubin, France) were anaesthetised with pentobarbital (40 mg/kg, i.p.). A polyethylene catheter was inserted into the abdominal aorta via a femoral artery and a venous catheter placed into a jugular vein for drug injection. Through a laparotomy, the bladder was exposed and, via an incision in the bladder wall, another polyethylene catheter was positioned into the urethra below the bladder neck and held in place by a suture on the bladder wall. Such a positioning of the urethral catheter does not interfere with normal micturition (Martin et al., 1995). The animals were allowed to recover for 48 hr before drug testing. At the day of the experiments, the animals were partially restrained in a restraining device and mean arterial BP, HR and UP were continuously monitored.

A control period of at least 20 min was established before i.v. drug injection. Seven experimental groups were randomly assigned for vehicle or drug treatment (n = 4–7 per group). Compounds were given as a single dose infused i.v. over 5 min and effects were analyzed at 5, 15, 30 and 60 min. Pressure changes were expressed as percentage changes from baseline values and statistical significance assessed by a one-way analysis of variance. Dose range of compounds was selected according to effects on urethral pressure and the uroselectivity profile of alfuzosin, doxazosin, tamsulosin (3, 10, 30 and 100 μg/kg), prazosin (3, 10 and 100 μg/kg), 5-Me-urapidil (30, 100 and 300 μg/kg) and terazosin (10, 30 and 100 μg/kg) were investigated.

Estimation of Uroselectivity

The simultaneous measurement of BP and UP in the same animal allows us to propose a definition of uroselectivity based on a reduction in UP without modification in BP (full uroselectivity), a reduction in UP associated with a decrease in BP less than 10% (partial uroselectivity) or a decrease in UP (or no modification of UP) associated with a decrease in BP equal or greater than 10% (no uroselectivity).

Compounds Used

All tested adrenoceptor antagonists were synthesized at Synthelabo Recherche (Rueil-Malmaison, France), except for 5 Me-urapidil which was obtained from Research Biochemicals International (Ik dcirich, France). All compounds were dissolved in normal saline or in a 5% glucose solution. Phenylephrine hydrochloride was obtained from Sigma Chemical Co. (St Louis, MO) and [3H]-prazosin from Amersham (Les Ulis, France).
Results

In vitro. Phenylephrine (0.1-300 µM) produced a concentration-dependent contraction of rabbit isolated prostate strips with a pEC$_{50}$ of 5.02 ± 0.08. All the antagonists investigated produced parallel, rightward shift of the phenylephrine E/[A] curve, indicative of competitive antagonism (fig. 1). The antagonist pK$_{B}$ estimates are given in table 1. The affinities ($pK_{i}$) for the three cloned alpha-1-adrenoceptor subtypes measured by [3H]prazosin binding displacement.

Fig. 1. Effects of alpha-1-adrenoceptor antagonists on phenylephrine-induced contractions of rabbit prostatic strips. Results are expressed as percentage of the maximum response to phenylephrine in the absence of adrenoceptor antagonists (%E$_{\text{max}}$ phenylephrine).
are summarized in Table 1. Among the tested compounds, only tamsulosin and 5-Me-urapidil showed alpha-1a/alpha-1b selectivity (ratio = 15.8 and 47.9, respectively) and smaller alpha-1a/alpha-1d selectivity (ratio = 2.7 and 13.8, respectively). All the other antagonists did not show any selectivity for the alpha-1a-adrenoceptor subtype or had a selectivity ratio inferior to unity.

When the antagonist potencies of these compounds (pK\textsubscript{B}) were compared with the affinity values at the three cloned alpha-1-adrenoceptor subtypes, no significant correlations were found between the antagonist affinities for hamster alpha-1b-adrenoceptors (r = 0.04, NS) or rat alpha-1d-adrenoceptors (r = 0.71, NS) and the pK\textsubscript{B} values obtained in rabbit prostate. In contrast, the antagonist potencies in rabbit prostate in vitro were highly correlated with the pK\textsubscript{B} values for the bovine alpha-1a-adrenoceptor subtype (r = 0.89, P < .05). However, the pK\textsubscript{B} values were consistently smaller (by 0.6 to 1.9 log unit) than the pK\textsubscript{B} values for the alpha-1a-adrenoceptor subtype, a result that suggests that the alpha-1-adrenoceptor mediating urethral contractions does not have all the characteristics of the alpha-1a-adrenoceptor. It should also be noted that the difference between antagonist potency and affinity for the alpha-1a-adrenoceptor is greater for the four quinazolines tested (alfuzosin, doxazosin, prazosin and terazosin) than for tamsulosin and 5-Me-urapidil.

**In vivo.** Evaluation of uroselectivity was carried out in conscious male rats by the simultaneous measurement of blood and urethral pressures. Throughout the observation period (60 min) no significant changes occurred in the vehicle-treated group (fig. 2: baseline: BP = 118.6 ± 3.6 mmHg, UP = 10.9 ± 1.3 cm H\textsubscript{2}O, HR = 448 ± 28 beats/min; at 60 min postdose BP = 118.9 ± 2.9 mmHg, UP = 10.4 ± 1.0 cm H\textsubscript{2}O, HR = 408 ± 19 beats/min, n = 11 for all parameters except for HR, n = 4). Base-line values of all parameters in the various experimental groups were not different (data not shown). HR was not significantly modified by any of the drugs studied (table 2).

At 3 µg/kg, alfuzosin did not modify UP or BP (fig. 3). At 10 µg/kg alfuzosin transiently decreased UP by 27.4 ± 9.7% at 5 min (P < .05) post-dose without modifying BP and no statistically significant changes were observed at other time points. At 30 µg/kg a decrease in urethral pressure (41.8 ± 3.6% at 5 min, P < .05) was observed and maintained for at least 60 min (−29.8 ± 4.4%, P < .05). This effect was accompanied by a transient effect on BP (−8.5 ± 3.2% at 5 min, P < .05) which waned after 15 min. At 100 µg/kg, UP was decreased by 26.9 ± 3.8% (P < .05) at 5 min and this effect lasted for at least 60 min (−23.0 ± 4.5%, P < .05). Meanwhile, BP was slightly decreased for 30 min (−9.8 ± 2.5% at 5 min and −5.4 ± 1.8% at 30 min, P < .05). It should be noticed that the maximum reduction in UP was already obtained at 30 µg/kg.

At 5 µg/kg, doxazosin transiently reduced UP by 18.0 ± 8.2% at 5 min (fig. 3, P < .05) without modifying BP, whereas at 10 µg/kg, no significant changes on either pressures occurred. At 30 µg/kg, UP was decreased at 5 min by 27.9 ± 10.3% (P < .05) whereas BP remained unchanged (−1.0 ± 2.9%, NS). At 100 µg/kg the reduction in UP at 5 min (−38.5 ± 7.3%, P < .05) was accompanied by a decrease of BP by 15.9 ± 4.0% (P < .05). The reduction in urethral pressure and in blood pressure was maintained up to 60 min. No

### Table 1

<table>
<thead>
<tr>
<th>Drug</th>
<th>Antagonism of Phenylephrine-Induced Contraction of Rabbit Prostate (pK\textsubscript{B})</th>
<th>Inhibition of [3H]-Prazosin-Binding (pK\textsubscript{B})</th>
<th>Receptor Subtype Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Bovine alpha-1a</td>
<td>Hamster alpha-1b</td>
</tr>
<tr>
<td>Alfuzosin</td>
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<td>Doxazosin</td>
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<td>Prazosin</td>
<td>8.15 ± 0.13 (n = 4)</td>
<td>9.73</td>
<td>10.18</td>
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<tr>
<td>Tamsulosin</td>
<td>9.74 ± 0.05 (n = 11)</td>
<td>10.40</td>
<td>9.20</td>
</tr>
<tr>
<td>Terazosin</td>
<td>7.46 ± 0.09 (n = 3)</td>
<td>8.53</td>
<td>9.16</td>
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<tr>
<td>5-Me-urapidil</td>
<td>8.29 ± 0.09 (n = 9)</td>
<td>8.89</td>
<td>7.21</td>
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</table>

**TABLE 2**

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Dose (µg/kg)</th>
<th>Heart Rate (bpm)</th>
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</thead>
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<td></td>
<td>Control</td>
<td>5 min post-treatment</td>
</tr>
<tr>
<td>Alfuzosin</td>
<td>10</td>
<td>490 ± 26</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>440 ± 38</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>394 ± 8</td>
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<tr>
<td>Doxazosin</td>
<td>3</td>
<td>395 ± 25</td>
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<td></td>
<td>10</td>
<td>428 ± 10</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>422 ± 24</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>425 ± 33</td>
</tr>
<tr>
<td>Prazosin</td>
<td>3</td>
<td>423 ± 23</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>409 ± 18</td>
</tr>
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<td></td>
<td>100</td>
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<td>Tamsulosin</td>
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<td></td>
<td>100</td>
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<tr>
<td></td>
<td>30</td>
<td>483 ± 5</td>
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<td>100</td>
<td>423 ± 34</td>
</tr>
<tr>
<td></td>
<td>300</td>
<td>420 ± 12</td>
</tr>
</tbody>
</table>

Heart rate values are expressed as mean ± S.E.M. (n = three to five per group). No significant differences exist between control (before drug infusion) and 5 min after treatment.
differences in maximal reductions of urethral pressure were seen between 30 and 100 μg/kg.

Prazosin (fig. 3), at 5 min post-dosing, induced a significant decrease (P < .05) in UP by 19.6 ± 3.6, 29.8 ± 8.6 and 19.3 ± 5.3% at 3, 10 and 100 μg/kg whereas BP was decreased (P < .05) by 10.3 ± 3.0, 9.5 ± 1.6 and 22.4 ± 6.7%, respectively. Decreases in urethral pressure were of variable duration, depending on the dose used, but in most cases were rather long lasting and associated with significant decreases (P < .05) in BP still present at 60 min post-dose at the three doses (−9.5 ± 4.7, −5.8 ± 1.1 and −14.9 ± 1.7%, respectively).

At 10 μg/kg, terazosin was without significant effects whereas at 30 and 100 μg/kg, BP was significantly decreased (−9.3 ± 1.5%, −19.2 ± 1.4% at 30 and 100 μg/kg, 5 min postdose, P < .05; fig. 3). Reduction of blood pressure lasted throughout the observation period (−8.2 ± 3.4 and −12.5 ± 4.1% at 30 and 100 μg/kg, 60 min post-dose, P < .05). Effects on UP were weak, variable and reached statistical significance only at 60 min post-dose in the 30 μg/kg group (−39.9 ± 5.9%).

Up to the dose of 300 μg/kg, 5-Me-urapidil (fig. 2) did not significantly modify BP. Variable effects were observed on UP and only a transient significant effect was obtained at 5 min post-dose in the 100 μg/kg group (−14.4 ± 5.9%, P < .05; fig. 2).

Tamsulosin decreased both UP and BP over the dose-range tested (fig. 2). At 3 μg/kg, no effects on UP were observed but a significant and transient decrease in BP (−15.0 ± 5.5% at 5 min, P < .05) was present. At 10, 30 and 100 μg/kg, UP was decreased (P < .05) at 5 min by 36.9 ± 6.4, 28.1 ± 4.7 and 24.2 ± 4.7%, respectively, and BP was decreased (P < .05) by 13.4 ± 4.8, 18.8 ± 4.8 and 21.3 ± 2.0%. Vascular effects lasted for at least 60 min whereas those on UP persisted at 10 μg/kg and waned after 15 min at the higher doses. Therefore, when present, decreases in UP were always accompanied by decreases in BP (fig. 2).

According to the proposed definition of functional uroselectivity, terazosin and 5-Me-urapidil did not consistently show uroselectivity whereas tamsulosin and prazosin show a partial uroselectivity only at some time points. Alfuzosin and doxazosin were fully uroselective at the two lower active doses.

**Discussion**

Alpha-1 adrenoceptor classification has evolved over the past years and although today the three cloned subtypes, i.e., alpha-1a, alpha-1b and alpha-1d are well characterized, their tissue distribution and function remain to be established. The specific contribution of alpha-1A-adrenoceptors to prostatic contractility has been intensively investigated due to the availability of new adrenoceptor antagonists with variable degree of selectivity for this subtype (Michel and Insel, 1994; Kawabe, 1995; Testa et al., 1994, 1996). Tamsulosin was one of the first antagonists for which selectivity for the alpha-1A-adrenoceptor subtype was reported (Michel et al., 1993) with selectivity ratios for the alpha-1a over the alpha-1b and alpha-1d-adrenoceptor ranging between 12 to 38 and 1 to 10, respectively (Michel et al., 1993, Ford et al., 1996). 5-Me-urapidil has been described as having high selectivity for the alpha-1a-adrenoceptor with selectivity ratios for the alpha-1a over the alpha-1b subtype ranging from 45 to 83 (Faure et al., 1994; Forray et al., 1994). Attempts to evaluate the relationship between selectivity for a given alpha-1-adrenoceptor subtype and functional in vitro and in vivo selectivity for the urinary tract led to different conclusions. They depend on the compounds evaluated, the type of receptors used to estimate affinities (cloned vs. native, hu-
man vs. animal) and the way selectivity was assessed (in vitro or in vivo). The binding data described in our study are in agreement with the values previously published for human cloned alpha-1-adrenoceptor subtypes and confirm the selectivity of tamsulosin and 5-Me-urapidil for the alpha-1a-adrenoceptors (Kenny et al., 1996).

In our study, the alpha-1-adrenoceptor antagonists tested dose-dependently shifted the dose-response contraction curves to phenylephrine of rabbit prostatic tissue. The antagonist affinities ($pK_B$) were well correlated with affinity for the cloned alpha-1a-adrenoceptor, and agree with previous data reported for human (Forray et al., 1994, Marshall et al., 1995), rat (Chess-Williams et al., 1994), rabbit (Auguet et al., 1995) or dog (Kenny et al., 1996; Testa et al., 1993) lower urinary tract tissues. These results suggest that alpha-1A-adrenoceptors may mediate phenylephrine-induced contractions of lower urinary tract tissues.

However, more recent studies have suggested that the characteristics of the functional alpha-1-adrenoceptor subtype in human prostate are not consistent with those of the alpha-1A-adrenoceptor subtype. This functional alpha-1-adrenoceptor subtype seems to better correspond with a sub-

**Fig. 3.** Time-course effects of nonselective alpha-1-adrenoceptor antagonists on urethral (filled symbols) and arterial blood pressure (open symbols) in conscious male rats. All drugs were administered by the i.v. route over a 5-min period. Results are expressed as percentage variation from control readings obtained before drug infusion (% variation).
type having low affinity for prazosin (Muramatsu et al., 1994) which is discriminated by RS-17053 (Ford et al., 1996). The data obtained with RS-17053 by Ford et al. (1996), and further confirmed by Kenny et al., (1996) with additional selective antagonists and by us (Van Der Graaf et al., 1996) clearly indicated that cloned alpha-1a-adrenoceptors and alpha-1-adrenoceptors mediating contractile responses to norepinephrine in vitro were different. In our study, the pK$_H$ values, expressing efficacy of the tested compounds to relax phenylephrine-induced contractions, are consistently lower (from 0.6 to 1.9 log unit) than the pK$_V$ values expressing the affinity of this drugs for the alpha-1a-adrenoceptor and this difference was indeed greater for the quinazoline compounds. The actual potency displayed by the antagonists tested is therefore 4- to 80-fold lower than their affinity for the alpha-1a-adrenoceptor and this shift could suggest that the receptor mediating smooth muscle contraction of the urethra does not have all the characteristics of the alpha-1a-adrenoceptor subtype. These results are also in agreement with those reported by Ford et al. (1996a, 1996b), Van Der Graaf et al. (1996) and Muramatsu et al. (1994) suggesting the involvement of the alpha-1L-adrenoceptor in the contraction of the lower urinary tract tissue.

To further evaluate the functional role of alpha-1-adrenoceptor subtypes, in the lower urinary tract, comparative in vivo studies with selective antagonists were carried out. Indeed, published data on respective effects on vasculature and lower urinary tract do not allow us to draw conclusions concerning functional uroselectivity. Few direct comparisons of in vivo efficacy and uroselectivity of the existing alpha-1-adrenoceptor antagonists are available. In the anesthetized dog, Kenny et al. (1994) showed that the potencies of several alpha-1a-adrenoceptor antagonists to inhibit the phenylephrine-induced increases in prostatic pressure were similar to their antagonist effect on increased blood pressure. In this study, 5-Me-urapidil was the only adrenoceptor antagonist to show uroselectivity, providing further contrast between the dog and the rat studies. However, Testa et al. (1994) showed that tamsulosin and rec15/2739 inhibited noradrenaline-induced increases in prostatic pressure with a respective selectivity ratio of 10 and 100 over the reduction in basal blood pressure. Accordingly, Shibashaky et al. (1992) showed in female dogs that R(–)YM 12617 (tamsulosin) was more potent to reduce phenylephrine-induced increases in urethral than arterial blood pressure. The use of agonists with a different specificity for alpha-adrenoceptor subtypes (phenylephrine vs. noradrenaline) or end organ responses (prostatic urethra vs. urethra) may account for such discrepancies. Recently, Brun et al. (1996), investigated in conscious dogs, the effects of tamsulosin, doxazosin and terazosin on phenylephrine-induced increases in UP and BP and reported a weak uroselectivity for tamsulosin at one of the doses tested. Alfuzosin, but not prazosin, was shown to be uroselective when its effects on blood pressure in spontaneously hypertensive rats were compared to its effects on electrically stimulated urethral pressure in cats (Lefèvre-Borg et al., 1993). In anesthetized cats, doxazosin and terazosin were shown to be active on the sympathetic drive to the bladder and on blood pressure within the same dose range, even though doxazosin induced less tachycardia than terazosin (Ramage et al., 1995). In all these studies, with the exception of the latter, adrenoceptor antagonists were tested against increases in urethral and arterial blood pressure induced by agonist injection, electrical stimulation or against a genetically induced hypertension. Our study, as well as a previous one (Martin et al., 1995), are to our knowledge, first attempts to evaluate the direct effects of alpha-1-adrenoceptor antagonists in conscious animals under normal adrenergic tone. The obtained results, together with antagonist affinities (pK$_V$) therefore provide new information on the functional role of alpha-1-adrenoceptor subtypes.

In our study we found that the two compounds with the highest affinity for the alpha-1a-adrenoceptor subtype, tamsulosin (pK$_V = 10.4$) and prazosin (pK$_V = 9.73$) were the most potent in affecting blood pressure as from the 3 μg/kg dose and the least uroselective. Compounds with higher functional uroselectivity, i.e., alfuzosin and doxazosin have a similar binding profile which is devoid of alpha-1-adrenoceptor subtype selectivity. 5-Me-urapidil was the compound with the highest selectivity for the alpha-1a-adrenoceptor subtype and, in our work, was devoid of significant activity on urethral and blood pressures. Its affinity for the alpha-1a-adrenoceptor subtype (pK$_V = 8.29$) was similar to that of doxazosin and, if this subtype was functionally relevant, an effect should have been seen at the doses tested (up to 300 μg/kg). Terazosin only induced minimal changes on urethral pressure at the intermediate dose we tested whereas all other compounds studied had a significant effect on urethral pressure at this dose. Other studies have clearly demonstrated the efficacy of terazosin to reduce urethral pressure. Nevertheless, all previous studies were carried out under conditions where urethral pressure was increased either by electrical stimulation (Lefèvre-Borg et al., 1993) or agonist infusion (Brun et al., 1996). It is not clear, whether the weakness of effect seen in our study is related to the absence of urethral hypertonia or due to differences in plasma clearance or plasma protein binding. Finally, no clear dose-response relationship was observed on urethral pressure, mainly between the two higher doses tested. At the higher dose tested, a marked decrease in blood pressure was obtained and it can be hypothesized that the vascular responses have blunted the urethral responses by decreasing the drug availability for the urethral tissue.

In our study, the selectivity for the alpha-1a-adrenoceptor subtype has been assessed using cloned bovine receptors and functional uroselectivity in conscious rats. The question of species differences could therefore be raised as a putative explanation for this lack of relationship between alpha-1a-adrenoceptor selectivity and functional uroselectivity. Affinities for the alpha-1a-adrenoceptor subtype of a variety of alpha-1-adrenoceptor antagonists are similar whether evaluated in native tissue (Testa et al., 1996), in cloned bovine receptors (Testa et al., 1996) or in human cloned receptors (Testa et al., 1995; Kenny et al., 1996). It seems therefore unlikely that species differences in binding data were of importance.

In conclusion, our results demonstrate that functional uroselectivity of adrenoceptor antagonists cannot be extrapolated from either receptor affinity or receptor subtype selectivity data. In the conscious male rat under normal adrenergic tone, the most uroselective drugs were alfuzosin and, over a more limited dose-range, doxazosin whereas tamsulosin, 5-Me-Urapidil, prazosin and terazosin where either partially uroselective or not uroselective. This uroselectivity...
is therefore not correlated with a selective affinity for the alpha-1-adrenoceptor subtype.

Acknowledgments
The technical assistance of C. Duquenne and V. Deplanne is gratefully acknowledged.

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