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Ketanserin versus urapidil: age-related cardiovascular effects in conscious rats

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Abstract

To examine whether serotonin (5-hydroxtryptamine, 5-HT)-mediated mechanisms for regulating blood pressure are influenced by advancing age, the cardiovascular effects of ketanserin and urapidil were compared in two groups of conscious rats at ages 4 (young) and 24 (old) months. Old rats had higher mean pressures but the same basal heart rates as young rats prior to drug treatment. Subsequent treatment with either ketanserin or urapidil produced similar cardiovascular effects. Both drugs in doses of 10 mg/kg i.v., lowered mean pressures more markedly in old than in young rats, and the larger hypotensive response in old rats was statistically significant even when expressed as percent reductions. Because drug treatment abolished the mild hypertension initially present in old rats, ensuing blood pressure levels no longer differed between age groups. On the other hand, neither drug had any appreciable effects on basal heart rate or angiotensin-induced reflex bradycardia at any age. Consequently, hypotensive enhancement in old rats cannot be due to age-related changes in reflex bradycardia. Inasmuch as ketanserin and urapidil, despite their differing modes of action on 5-HT receptors, were both equally adept at lowering blood pressure more in old rats, these results suggest that enhancement occurs selectively only with 5-HT-mediated hypotension. Thus, unlike other antihypertensive drugs (like prazosin or lisinopril) whose modes of action do not include 5-HT mediation and whose hypotensive effects do not increase with age, our results suggest that hypotensive responses to ketanserin and urapidil are selectively enhanced because of their actions on 5-HT receptors.

Keywords: Aging; Angiotensin; Blood pressure; Heart rate; Ketanserin; Reflex bradycardia; Urapidil

1. Introduction

Antihypertensive drug treatment was once considered potentially detrimental in the elderly, but is now widely accepted to reduce cardiovascular morbidity and mortality in hypertensive patients over 60 years old (Dahlöf et al., 1991; Kostis et al., 1997; MRC Working Party, 1992; SHEP Cooperative Research Group, 1991; Staessen et al., 1997). Ketanserin and urapidil differ from other antihypertensive drugs not only because they lower blood pressure more strongly in elderly hypertensives, but also because they act partly through endogenous serotonin (5-hydroxtryptamine, 5-HT). Thus, ketanserin lowers blood pressure more effectively in elderly hypertensives (De Crée et al., 1985; Doyle, 1988) while urapidil, lowered blood pressure more than did diuretics or β-adrenergic antagonists in more than 5000 elderly hypertensives (Hansson, 1994; Hansson and Petitet, 1995). Vasodilation, which commonly occurs with both drugs, is due to α-adrenergic and 5-HT mechanisms. Indicative of α_1-adrenergic antagonism, pressor responses to methoxamine (Kalkman et al., 1982) or phenylephrine (Davidow and Buñag, 1996; Goering and Zimmerman, 1986) are inhibited by both drugs. But on 5-HT receptors their actions differ as urapidil is a 5-HT_{1A} receptor agonist (Gillis et al., 1987; Grob et al., 1987; Steinbusch et al., 1990) while ketanserin is a 5-HT_2 receptor antagonist (Davidow et al., 1994; Davy et al., 1987; Persson et al., 1982; Smits et al., 1988; Van Nueten et al., 1981).

Brain 5-HT may participate in the baroreflex impairment that occurs with aging (Gribbin et al., 1971). 5-HT neurons in raphe nuclei project widely to other brain areas (Jacobs and Azmitia, 1992) and cortical 5-HT_{1A} and 5-HT_{2A} binding sites are reduced with aging (Meltzer et al., 1998). 5-HT

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content in brains of old rats is not altered equally because it increases in medullary raphe nuclei (Steinbusch et al., 1990) but decreases in the hypothalamus (Gozlan et al., 1990). 5-HT injected into the nucleus tractus solitarius decreases mean pressure, heart rate, and renal nerve and because these effects are less pronounced in 24-month- than in 2-month-old rats desensitization of 5-HT mechanisms in the nucleus tractus solitarius with increasing age seems likely (Itoh and Buñag, 1992). Because 5-HT_2 pressor responses are reduced while 5-HT_3 bradycardic responses are enhanced (Davidow et al., 1994), these two responses combined, could increase the hypotensive effects of ketanserin in old rats.

The present studies aimed to use urapidil and ketanserin as tools to test whether different modes of 5-HT action (i.e., 5-HT_{1A} receptor agonist activation with urapidil versus 5-HT_2 receptor antagonism with ketanserin) would produce different age-related cardiovascular effects. Because previous studies had shown that 10 mg/kg i.v. doses of ketanserin (Kalkman et al., 1982; Smits et al., 1988; Widdop et al., 1990) or urapidil (Valenta et al., 1980) lowered blood pressure consistently, hypotensive effects produced by i.v. infusion of doses ranging from 5 to 20 mg/kg were measured in preliminary experiments on 4-month-old rats. Ensuing reductions in blood pressure produced by 5 were smaller with than those by 10 mg/kg doses, but did not increase further at the 20 mg/kg dose. As this indicated that i.v. infusion of 10 mg/kg doses of either ketanserin or urapidil had maximal hypotensive effects, 10 mg/kg doses were infused routinely. Upon finding that the hypotensive effects of both drugs were larger in 24-month- than in 4-month-old rats, subsequent experiments were done to examine whether age-related effects on reflex bradycardia were related to the enhanced hypotensive responsiveness occurring in old rats.

2. Materials and methods

Forty-seven male Sprague–Dawley rats purchased from Harlan Sprague–Dawley (Indianapolis, IN) in two age groups are henceforth referred to either as "young" (37 rats, 4 months old) or "old" (10 rats, 24 months old). Preliminary experiments were done on 27 young rats to measure direct cardiovascular effects of ketanserin or urapidil ($n=16$) and reproducibility of angiotensin-induced reflex bradycardia during repeated testing ($n=11$). Reproducibility of responses to successive infusions of angiotensin was determined because reflex bradycardia had to be elicited by repeated infusions of angiotensin in the same rat. Based on the preliminary findings (i.e., that reflex bradycardia was more reproducible between the second and third infusions), baroreflex effects of urapidil and ketanserin were assessed by comparing reflex bradycardia elicited during the second and third infusions. To then assess age-related changes produced by ketanserin or urapidil treatment on angiotensin-induced reflex bradycardia, angiotensin responses were compared in 10 young and 10 old rats. This was done by recording six angiotensin responses in each rat as follows: (1) three tests on week 1 done before pretreatment, after infusing saline vehicle, and after infusing ketanserin in half of the rats and urapidil in the others; and (2) three tests on week 2 after switching drug treatments (i.e., the same tests were repeated to obtain data for both drugs in every rat by treating those previously treated with ketanserin with urapidil and vice versa).

2.1. Surgical implantation of indwelling cannulas

To record cardiovascular drug effects while the rats were conscious, indwelling femoral cannulas for recording blood pressure and infusing drugs were implanted chronically in each rat 1 week before testing. Each rat was transiently anesthetized with sodium pentobarbital (55 mg/kg, i.p.) while indwelling cannulas filled with heparinized saline (30 U/ml) were inserted separately into the left femoral artery for blood pressure recording, and into the ipsilateral vein for drug infusions (Buñag and Davidow, 1996; Buñag et al., 1990a,b). Cannulas consisted of polyethylene tubing: 3–5 cm of PE-10 threaded and heat-fused into 13–18 cm of PE-50. The inner end of PE-10 tubing was inserted into the artery or vein while the outer end of PE-50 tubing was tunneled subcutaneously, exteriorized at the nape, and sealed with a 23-ga plug. To allow enough time for postoperative recovery, all rats were left untouched for 7 days in individual plastic cages in an air-conditioned room with unrestricted access to food (Rodent Laboratory Chow, Ralston Purina, St. Louis, MO) and water.

2.2. Recording cardiovascular responses to intravenous drugs in conscious rats

All drug responses were recorded from indwelling femoral arterial cannulas 7–14 days after cannulation to avoid artifacts caused by anesthesia (Barringer and Buñag, 1990; Buñag and Davidow, 1996). While each conscious rat was kept in its own open-topped plastic cage, pulsatile pressure was recorded by connecting the arterial cannula through PE-50 tubing to a small-volume-displacement pressure transducer (P10 EZ, SpectraMed, Oxnard, CA) placed outside the cage at the same level as the rat. Analog signals for mean arterial pressure and heart rate were derived from the pulsatile pressure signal using a cardiovascular analyzer (CVA-1 Buxco Electronics, Sharon, CT). Rats were left undisturbed for the first 30 min to allow blood pressure and heart rate to return to resting levels.

Cardiovascular effects of ketanserin or urapidil were recorded in 16 young rats after injecting 10 mg/kg doses (2.0 ml of 5 mg/ml drug solutions) into the venous catheter. Catheters were flushed with 0.6 ml (deadspace volume) isotonic saline solution after each injection. Effects on angiotensin-induced reflex bradycardia were recorded in

20 other rats (i.e., 10 young and 10 old) pretreated with ketanserin or urapidil an hour before the third baroreflex test on week 1 or 2. In each age group, five rats were treated with ketanserin on the first week and then with urapidil a week later; the other five were treated first with urapidil and then with ketanserin a week later.

Reflex bradycardia was elicited by infusing angiotensin IV to elevate systemic pressure. Venous catheters were connected to plastic syringes mounted on a computer-driven infusion pump (model 22, Harvard Apparatus, South Natick, MA). Angiotensin infusion rates were programmed to increase progressively from 23 to 117 μl/min/100 g body weight in 50 steps each lasting for 1.0 s (Buñag et al., 1990a). Doses of 0.115 to 5.85 μg/min/kg, delivered by infusing total volumes of 2–4 ml/kg over 50 s, produced maximal increases in mean pressure of 50–65 mm Hg.

2.3. Data acquisition and analysis

A data acquisition system consisting of a computer, 12 bit A/D board (DT 2801, Data Translation, Marboro, MA), WFS hardware scroller and programs for data acquisition (DATAQ Instruments, Akron, OH) were used to digitize analog outputs from the cardiovascular analyzer (Buñag et al., 1990b). Digitized data was stored in files from which corresponding units in mm Hg for mean pressure and bpm for heart rate were determined. Before each recording, pressure calibrations were checked and zero levels adjusted using a mercury manometer.

Data points obtained from each recording by reading mean pressure and heart rate every second during the infusion period were smoothed using the Blackman window filter function with a cutoff frequency of 0.1 (Buñag and Davidow, 1996; Buñag et al., 1990a,b). Values recorded immediately before infusions began were averaged to obtain preinfusion baseline levels while those recorded for 50 s during infusion were used to calculate drug-induced reflex responses. Data thus obtained were analyzed first by averaging mean pressure and heart rate changes produced by infusing progressively increasing drug doses, and then calculating linear regression slopes.

2.4. Drugs, doses and statistics

Drug doses are expressed as the amount of the salt per kilogram body weight. Angiotensin II acetate (Sigma, St. Louis, MO) was infused i.v. for eliciting reflex bradycardia. A single 10 mg/kg dose for either ketanserin or urapidil was tested routinely based on previous studies showing that 10 mg/kg i.v. doses of ketanserin (Kalkman et al., 1982; Smits et al., 1988; Widdop et al., 1990) or urapidil (Valenta et al., 1980) lower blood pressure consistently in rats. Ketanserin tartrate was generously supplied by Janssen Pharmaceutica (Beerse, Belgium) while urapidil hydrochloride was purchased from Research Biochemicals International (Natick, MA). Bacteriostatic sodium chloride 0.9% was used as the vehicle for all drug solutions and for follow-up flushing of all intravenous infusions.

All data are expressed as averages ± S.E.M. Baseline values for mean pressure, heart rate, and body weight, were compared using a two-factor (drug by time) analysis of variance (ANOVA; Bruning and Kintz, 1987). To eliminate variations caused by different time points of measurement during baroreflex tests involving infusions of angiotensin, drug induced changes in mean pressure and heart rate were compared using a three-way (age by drug by time) ANOVA. Whenever *F*-ratios significant at 5% or less were obtained, Newman–Keuls' multiple range test was used to determine the significance of differences between pairs of means (Bruning and Kintz, 1987).

3. Results

3.1. Direct blood pressure effects of ketanserin or urapidil

Following i.v. infusion of either ketanserin or urapidil, 10 mg/kg/min, in 16 young rats (i.e., eight for each drug), mean arterial pressures (mm Hg) fell from 116 ± 3 to 94 ± 4 with urapidil and from 110 ± 2 to 93 ± 3 with ketanserin. Heart

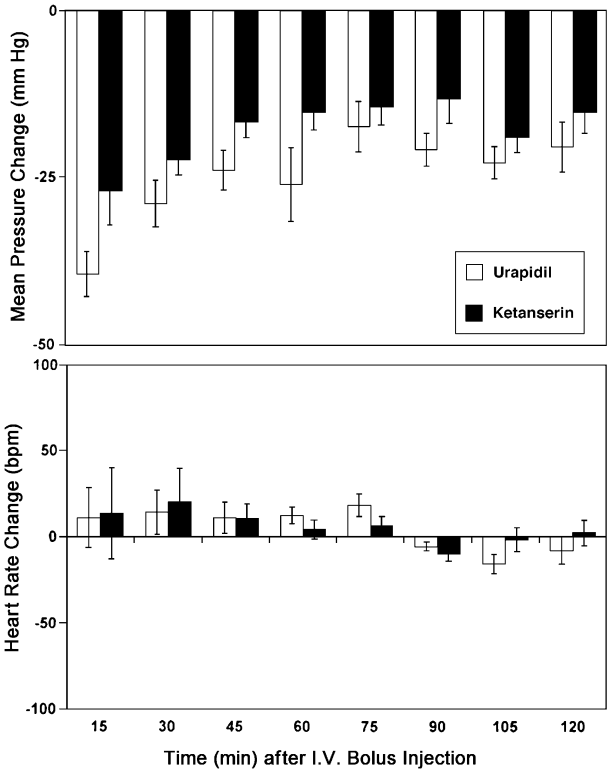

Fig. 1. Time course of mean pressure and heart rate changes occurring after i.v. infusion of 10 mg/kg doses of ketanserin (black bars) or urapidil (white bars) in 16 conscious young rats ($n = 8$ for each drug). Top panels of mean pressure in mm Hg (F-ratio 1.61, p-value > 0.2) and bottom panels of heart rate in bpm (F-ratio 0.15, p-value > 0.7). None of differences between bar pairs or treatment groups are significant; at each time point all p's > 0.1.

Table 1
Cardiovascular responses to three repeated intravenous infusions of angiotensin in 11 conscious young (4 months old) rats[a]

Infusion time (s)	Pressor response (mm Hg)			Reflex bradycardia (bpm)		
	Test 1	Test 2	Test 3	Test 1	Test 2	Test 3
5	4 ± 2	5 ± 1	3 ± 1	−4 ± 2	−3 ± 1	−1 ± 2
10	12 ± 3	11 ± 1	11 ± 1	−14 ± 4	−11 ± 3	−10 ± 3
15	23 ± 4	22 ± 2	23 ± 2	−29 ± 7	−27 ± 5	−30 ± 5
20	32 ± 4	34 ± 2	34 ± 3	−43 ± 9	−46 ± 8	−54 ± 8
25	40 ± 4	43 ± 3	43 ± 4	−53 ± 10	−62 ± 10	−70 ± 10
30	45 ± 4	49 ± 3	49 ± 4	−61 ± 11	−74 ± 11	−77 ± 11
35	51 ± 4	53 ± 3	55 ± 5	−66 ± 11	−86 ± 13	−81 ± 11
40	56 ± 5	57 ± 4	60 ± 5	−71 ± 12	−96 ± 14	−87 ± 12
45	60 ± 5	61 ± 4	63 ± 5	−76 ± 13	−105 ± 15	−93 ± 13
50	62 ± 5	63 ± 4	65 ± 5	−80 ± 14	−109 ± 16	−98 ± 14
F-ratio	1.74; $P>0.2$			15.39; $P<0.0001$		

[a] Average ± S.E.M. changes from baselines of: 116 ± 1 mm Hg for mean pressure and 342 ± 9 bpm for heart rate in test 1, 114 ± 3 mm Hg for mean pressure and 325 ± 10 bpm for heart rate in test 2, and 113 ± 3 mm Hg for mean pressure and 345 ± 12 bpm for heart rate in test 3. Baseline differences between tests are not significant (i.e., *F*-ratio of 0.47, $P>0.63$ for mean pressure and of 1.14, $P>0.33$ for heart rate).

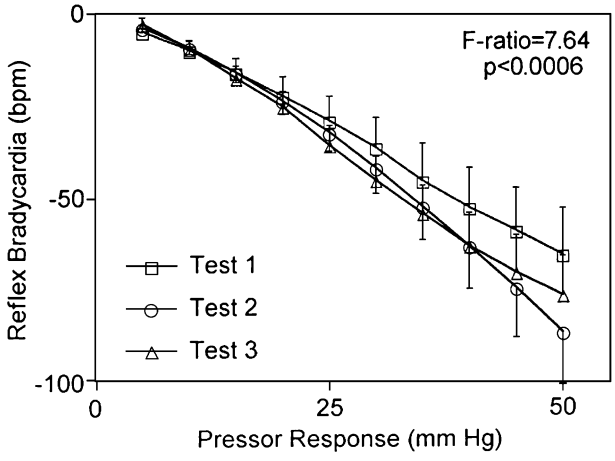

Fig. 2. Reflex bradycardia plotted against each 5 mm Hg increase in mean pressure during i.v. infusions of angiotensin based on data obtained on three separate tests in the same conscious young rats ($n=11$). Tests 1 and 2 were recorded 1 h apart on the seventh day after indwelling catheters were surgically implanted; test 3 was recorded a day later or on the eighth day after cannulation. Although sensitivity of reflex bradycardia was less on test 1, it did not differ between tests 2 and 3.

rates were unaffected: average changes (bpm) were from 362 ± 9 to 354 ± 9 for urapidil and from 350 ± 9 to 339 ± 7 for ketanserin. Peak hypotensive effects occurred within 15 min after which blood pressure slowly leveled off after 45–60 min (Fig. 1). By the second hour, both drugs had lowered mean pressure by about 20 mm Hg to almost the same level, and differences between treatment groups were not significant (all *p*-values >0.1 for each time point in Fig. 1). Based on these subsequent baroreflex tests were performed an hour after infusions of ketanserin or urapidil.

3.2. Sequence determination for baroreflex testing

To determine whether reflex bradycardic responses to angiotensin would remain unchanged upon repeated testing in the same rat, cardiovascular responses to 50-s i.v. infusions of angiotensin were recorded thrice on separate sessions: in 11 young rats (Fig. 2). Blood pressure increases produced by angiotensin were always accompanied by reflex bradycardia,

Table 2
Effects of ketanserin or urapidil in conscious young or old rats on baselines for mean pressure or heart rate

Treatment	Rat Age (month)	Cardiovascular Measurements			
		Before	After	Δ change	% change
(A) Mean pressure (mm Hg)					
Ketanserin	4	120 ± 1	105 ± 2	−15 ± 1	−12 ± 1
	24	140 ± 3[†]	109 ± 3	−31 ± 4[a]	−22 ± 3[a]
Urapidil	4	119 ± 1	100 ± 2	−19 ± 2	−16 ± 1
	24	137 ± 3[†]	104 ± 3	−33 ± 5[a]	−24 ± 3[a]
(B) Heart rate (bpm)					
Ketanserin	4	364 ± 12	388 ± 6	24 ± 13	8 ± 4
	24	386 ± 8	379 ± 8	−7 ± 11	−1 ± 3
Urapidil	4	377 ± 10	409 ± 8	32 ± 18	11 ± 7
	24	383 ± 7	378 ± 9	−5 ± 9	−1 ± 2

[a] $P<0.05$ as compared with corresponding average for young or 4-month-old rats.

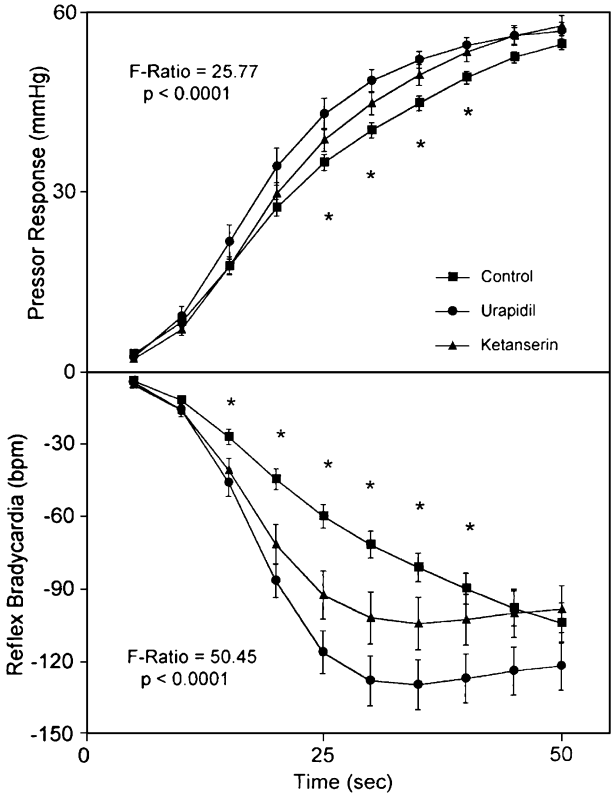

Fig. 3. Absolute increases in mean pressure (top panel) and reflex decreases in heart rate (bottom panel) produced in 10 conscious young (4 months old) rats by infusing angiotensin i.v. following pretreatment with saline vehicle, ketanserin, or urapidil. Asterisks indicate significant differences between treatment groups using Newman–Keuls' multiple range test.

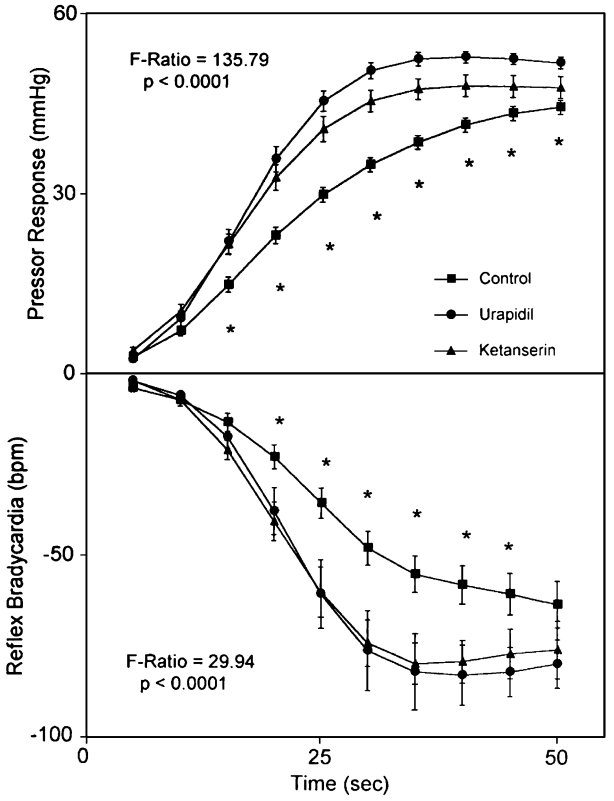

Fig. 4. Absolute increases in mean pressure (top panel) and reflex decreases in heart rate (bottom panel) recorded from 10 conscious old (24 months old) rats by infusing angiotensin i.v. following pretreatment with saline vehicle, ketanserin, or urapidil. Asterisks indicate significant differences between treatment groups using Newman–Keuls' multiple range test.

but although pressor responses did not differ from one test to another (F-ratio 1.74, p-value > 0.2; left half of Table 1), bradycardia was significantly less during the first test than during the other two tests (F-ratio 15.39, $p < 0.0001$; right half of Table 1). The magnitude of bradycardia plotted at each 5 mm Hg increase in mean pressure, was significantly lower during the first test (i.e., $p < 0.05$ compared with the second test and $p < 0.02$ compared with the third test), but almost identical during the last two tests ($p > 0.9$). Based on this subsequent pretreatment with ketanserin or urapidil was always done routinely between the second and third tests.

3.3. Larger hypotensive effects of ketanserin or urapidil in older rats

Initial baselines for mean pressure were significantly higher in old than in young rats, but those for heart rate did not differ between age groups (Table 2). Upon subsequent treatment with ketanserin or urapidil, blood pressure was always lowered more prominently in old than in young rats while heart rates, though slightly increased in young rats, still did not differ between age groups. Average decreases in pressure (mm Hg) were -15 ± 1 in young and -31 ± 4 in old rats (F-ratio = 13.06; $p < 0.002$) for ketanserin, and -19 ± 2 in young and -33 ± 5 in old rats (F-ratio = 8.66; $p < 0.01$) for urapidil. The same data expressed as percent reductions were -12 ± 1 in young and -22 ± 3 in old rats (F-ratio = 10.46; $p < 0.005$) for ketanserin, and -16 ± 1 in young and -24 ± 3 in old rats (F-ratio = 6.40; $p < 0.02$) for urapidil. Because hypotensive effects were unequivocally larger in old than in young rats, ensuing blood pressure levels no longer differed between age groups thereby indicating that drug treatment had abolished the mild hypertension initially present in old rats.

3.4. Age-related alterations by ketanserin or urapidil of angiotensin-induced reflex bradycardia

Reflex bradycardic responses to infused angiotensin recorded 1 h after pretreatment with either ketanserin or urapidil were always larger than those recorded before drug treatment. In young rats, pressor responses to angiotensin after ketanserin treatment were significantly larger at 35 and 40 s, and from 25 through 40 s after urapidil treatment, as compared with those after vehicle treatment (F-ratio comparing treatment groups = 25.77, $p < 0.0001$; Fig. 3 top panel). Reflex bradycardia was also significantly more pronounced from 15 through 35 s after ketanserin and from 15 through 40 s after urapidil (F-ratio comparing treatment groups = 50.45, $p < 0.0001$; Fig. 3 bottom panel). By contrast, in old rats although both mean pressure and heart rate responses also increased after either drug, the increases occurred earlier being significant for pressor responses from 15 through 45 s for ketanserin and from 15 through 50 s for urapidil (F-ratio comparing treatment groups = 135.79, $p < 0.0001$; Fig. 4 top panel), and for reflex bradycardia from 20 through 45 s for both drugs (F-ratio comparing treatment groups = 29.94, $p < 0.0001$; Fig. 4 bottom panel).

Regression coefficients obtained by plotting reductions in heart rate occurring with every 5 mm Hg increment in pressure (data in Table 2 expressed as percent changes to normalize baseline differences between age groups), ensuing slopes for bradycardia were always lower in old than in young rats (Table 3; F-ratio of 6.46 with p-value < 0.0001) thereby indicating that baroreflex responsiveness had diminished with

Table 3
Regression slopes for angiotensin-induced bradycardia in conscious young or old rats treated with ketanserin or urapidil[a]

Treatment groups	Regression slopes (% bpm/% mm Hg)	F-ratio; p-value
(A) Young (4 months old)		
Untreated	-0.598 ± 0.05	0.78l; $P > 0.5$
Ketanserin	-0.612 ± 0.07	
Urapidil	-0.700 ± 0.07	
(B) Old (24 months old)		
Untreated	-0.390 ± 0.05	0.430; $P > 0.6$
Ketanserin	-0.399 ± 0.04	
Urapidil	-0.329 ± 0.06	

[a] F-ratio of 6.46 comparing young versus old rats with $P < 0.0001$.

increased age. However, the changes produced by either urapidil or ketanserin within each age group were not significant. In young rats, although regression slopes for ketanserin and urapidil were slightly higher than in untreated controls, none of the differences between groups were significant (Table 3; F-ratio of 7.81 with p-value < 0.5). Similarly, among old rats regression slopes also varied slightly between untreated and treated groups, but group differences were also not significant (Table 3; F-ratio of 4.30 with p-value > 0.6). These results therefore indicate that while reflex bradycardia was consistently weaker in old than in young rats, within each age group pretreatment with either ketanserin or urapidil had no significant effects on reflex bradycardia.

4. Discussion

Ketanserin and urapidil had similar cardiovascular effects in the conscious rats studied here. Both drugs, in 10 mg/kg i.v. doses, lowered blood pressure more markedly in old than in young rats, and the larger hypotensive effect in old rats was statistically significant even when expressed as percent reductions (Table 2). Because of this ensuing blood pressure levels no longer differed between age groups thereby indicating that drug treatment had abolished the mild hypertension that was initially present in old rats. On the other hand, neither drug affected basal heart rate (Table 2) or angiotensin-induced reflex bradycardia (Table 3) at any age. The absence of chronotropic effects indicates that enhanced hypotensive responses in old rats was unrelated to changes in reflex bradycardia. Because hypotensive responses to both drugs were enhanced in old rats despite differences in their actions on 5-HT receptors, if enhancement commonly occurs only with 5-HT-mediated hypotensive responses then it could explain why responsiveness to ketanserin and urapidil increases with age while that to other antihypertensive drugs like prazosin (Davidow and Buñag, 1996) or lisinopril (Montemayor et al., 1997) does not.

Drug effects on reflex bradycardia in conscious rats are technically cumbersome to assess. Initial baseline pressures could have differed here because old rats initially had higher pressures than the young ones, and both ketanserin and urapidil had prolonged hypotensive effects. To compensate for such differences, we compared angiotensin-induced reflex bradycardia only when pressures following ketanserin or urapidil treatment had stabilized, and data were analyzed not only as absolute (Figs. 3 and 4) but also as percent changes (Table 3). Additionally, because initial angiotensin infusions elicited significantly less reflex bradycardia (Table 1 and Fig. 2), ketanserin or urapidil treatment was tested only between the second and third angiotensin infusions.

Because brain areas that normally regulate blood pressure are richly supplied with 5-HT containing neurons whose 5-HT content becomes altered by aging (Gozlan et al., 1990; Steinbusch et al., 1990), 5-HT mediated mechanisms could contribute to impair blood pressure regulation in the elderly. Of seven major 5-HT receptor subtypes, two have prominent blood pressure effects, namely: the 5-HT_{1A} and 5-HT_2 receptors in the rostral ventrolateral medulla (McCall and Clement, 1994). 5-HT_{1A} receptor agonists like urapidil lower blood pressure by inhibiting sympathetic nerves and stimulating the vagus. On the other hand, 5-HT_2 receptor activation causes peripheral vasoconstriction, and centrally increases sympathetic activity and vasopressin release, but central sympathoexcitation has been shown only in cats but not in rats (McCall and Clement, 1994). Moreover, 5-HT_{1A} receptors lower blood pressure through vasodilation and bradycardia caused by sympathetic inhibition (Nosjean and Guyenet, 1991) and vagal stimulation (Ramage et al., 1988), while 5-HT_2 receptors elevate blood pressure through vasoconstriction caused by increases in sympathetic nerve activity (McCall et al., 1987) and renal renin release (Alper, 1990). However, the similarity in enhanced hypotensive effects produced here in old rats by both drugs indicates that underlying 5-HT mechanisms cannot be clearly differentiated in intact rats.

An age-related reduction in reflex bradycardia could enhance hypotensive responses in old rats. Urapidil should have stronger effects on heart rate and reflex bradycardia than ketanserin because central vagal stimulation can be elicited from 5-HT_{1A} but not from 5-HT_2 receptors (McCall et al., 1987). However, the age-related heart rate changes seen here were highly variable. Whereas basal heart rates tended to increase in young but not in old rats following treatment with either urapidil or ketanserin, ensuing differences between rat groups were not significant (Table 2). Additionally, although ketanserin doses of 300 μg/100 g i.v. have previously been shown to enhance reflex bradycardia in old rats (Davidow and Buñag, 1996), with the 10 mg/kg i.v. doses used here, neither ketanserin nor urapidil had significant effects on reflex bradycardia (Table 3) whether the rats were young or old. Hence, the results now available do not support explanations based on direct or reflex changes in heart rate.

Alternatively, changes in adrenergic responsiveness with advancing age could participate since both ketanserin and urapidil can block α_1-adrenergic receptors (Davidow and Buñag, 1996; Goering and Zimmerman, 1986; Kalkman et al., 1982). Adrenergic desensitization may occur with increased age because in aging male rats pressor responses to phenylephrine or epinephrine are reduced while those to angiotensin are not (Buñag and Teravainen, 1991). Reduced adrenergic responsiveness in the elderly may be partly due to elevated plasma catecholamine levels (Esler et al., 1981; Sowers et al., 1983; Ziegler et al., 1976) which would increase receptor occupancy and down-regulate vascular adrenergic receptors. Subsequent α_1-adrenergic blockade could then enhance hypotension because old rats would have more catecholamines to block. This explanation is also unlikely (Davidow and Buñag, 1996), however, because hypotensive effects were age-related only for ketanserin but not for prazosin (which blocks α_1-adrenergic receptors without affecting 5-HT_2 receptors).

Finally, it may be possible that all drug-induced changes in blood pressure will be enhanced by impaired baroreflexes in old rats or elderly people. With advancing age, the ensuing reduction in reflex bradycardia lessens the ability of 24-month-old rats to buffer drug-induced hypotensive responses which would then be augmented. Supporting this explanation, hypotensive responses to ketanserin are augmented in sinoaortic denervated rats (Su et al., 1992). However, this interpretation would not explain why hypotensive responses to other antihypertensive drugs like prazosin (Davidow and Buñag, 1996) or lisinopril (Montemayor et al., 1997) are not enhanced in old rats.

In summary, although the mechanisms by which ketanserin and urapidil lower blood pressure more effectively in aging rats have yet to be identified, neither 5-HT-receptor mechanisms, changes in reflex bradycardia, nor α_1-adrenergic blockade can account for the age-related enhancement. Cardiovascular drug effects in old rats are complicated because the various components for regulating blood pressure might not be affected uniformly either by aging or by drugs like ketanserin or urapidil. Although ketanserin and urapidil, lower blood pressure more effectively in the elderly and in old rats, they cannot be used to differentiate age-related changes in 5-HT-mediated mechanisms in intact rats. Nonetheless, because hypotensive responses to both drugs were enhanced in old rats despite differences in their actions on 5-HT receptors, an age-related enhancement may be uniquely applicable only to 5-HT-mediated hypotensive responses and as such could explain why responsiveness to ketanserin and urapidil increases with age while that to other antihypertensive drugs like prazosin or lisinopril does not.

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