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Cardiovascular effects in the rat of ketanserin, a novel 5-hydroxytryptamine receptor blocking agent

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Following intravenous administration of ketanserin (0·3–10 mg kg^{-1}) to conscious or anaesthetized normotensive and spontaneously hypertensive rats there were dose-dependent blood pressure reductions but no compensatory tachycardia. Intracerebroventricular administration of ketanserin (25–500 μg) had inconsistent and largely insignificant cardiovascular effects. In a dose range where it produces hypotension ketanserin antagonized the pressor responses to adrenaline and noradrenaline as well as to 5-hydroxytryptamine in monoamine depleted and spinalized rats. It is suggested that the hypotensive action of ketanserin in the rat does not involve a central mechanism but a peripheral α-adrenolytic action is implicated.

Ketanserin has recently been introduced as a new specific 5-hydroxytryptamine (5-HT) receptor antagonist that inhibits [^{3}H]spiperone binding in rat brain (Leysen et al 1981) as well as the responses to 5-HT in blood vessels (van Nueten et al 1981). The compound reduces blood pressure in animals (van Nueten et al 1981) and hypertensive man (de Cree et al 1981) while eliciting no compensatory tachycardia. It has been suggested that ketanserin produces hypotension by blocking vascular 5-HT_2 receptors and conversely that peripheral 5-HT mechanisms by direct vasoconstriction or vascular sensitization to endogenous catecholamines may contribute to development of hypertension (see de Cree et al 1981; van Nueten et al 1981).

Since other 5-HT receptor antagonists, e.g. cyproheptadine, do not lower blood pressure in a similar manner (Antonaccio & Coté 1976) the present study was performed to examine the interactions of ketanserin with other monoamine receptors that participate in vascular control. Furthermore, in view of the lack of tachycardia to ketanserin, possible central actions of the compound were sought. Finally, considering the proposed hypersensitivity of the vascular smooth muscle to 5-HT in spontaneously hypertensive rats (SHR, Collins & Vanhoutte 1981), we investigated the cardiovascular responses to ketanserin in SHR as well as normotensive animals.

METHODS

Experiments were performed on adult (220–270 g) male Sprague-Dawley rats (SDR, Anticimex) and spontaneously hypertensive rats (SHR, Möllegaard).

Mean arterial blood pressure and heart rate were measured in conscious, unrestrained or anaesthetized rats through indwelling catheters (Portex tubing, PP 50, carotid artery) connected to Statham P23D transducers (Trolin 1975). For recording, a Grass Polygraph Model 7 was used.

Intravenous (i.v.) catheters (PP 50) were implanted into the right superior caval vein through the jugular vein. Intracerebroventricular (i.c.v.) catheters (PP 10) were implanted into each lateral cerebral ventricle 1–2 days before experimentation (Biswas & Carlsson 1977). I.c.v. injections consisted of 2–4 μl of drug solution followed by 6–8 μl of saline into each catheter at the rate of 10 μl min^{-1}.

The ability of ketanserin to interact with peripheral monoamine receptors was assessed in animals depleted of monoamines by reserpine pretreatment (10 mg kg^{-1} i.p., 6 h) and with their spinal cords transected at the level of C_7 (under ether anaesthesia, 4 h). A control blood pressure and heart rate response was obtained to i.v. administration of submaximal doses of noradrenaline (NA, 0·5 μg), adrenaline (A, 0·5 μg), 5-HT (25 μg) and isoprenaline (0·25 μg) before and after the i.v. injections of ketanserin. The maximal levels of responses were used in calculations. Each animal was used only for one dose of ketanserin.

Drugs. The drugs used were: ketanserin (R49945, courtesy of Janssen, Beerse, Belgium), reserpine (Ciba-Geigy, Mölndal, Sweden), noradrenaline bitartrate (Sigma, St Louis, U.S.A.), adrenaline bitartrate (Sigma), isoprenaline bitartrate (Sigma), 5-hydroxytryptamine sulphate (Aldrich, Milwaukee,

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U.S.A.). Ketanserin and reserpine were dissolved in a few drops of glacial acetic acid and the final volume made up of 5·5% glucose. The rest of the drugs were dissolved in 0·9% NaCl.

Statistics. Significances of differences were calculated by analysis of variance with two independent criteria for classification followed by Student's *t*-test or paired *t*-test alone.

RESULTS

Intravenously administered ketanserin (0·3–10 mg kg^{-1}) produced dose-dependent reductions of blood pressure which were immediate in onset and lasted from 30 min to several hours (Fig. 1). In the low dose-range (0·3–1·25 mg kg^{-1}) the blood pressure decrease seemed larger in SHR than in SDR but individual responses to low doses varied. At 2·5–10 mg kg^{-1} there were no differences between the two strains. Heart rate changes were insignificant.

The same amounts of ketanserin (0·3–10 mg kg^{-1}, n = 3–5) were given to SHR and SDR anaesthetized with chloral hydrate. Blood pressure reductions were of the same order of magnitude as in conscious animals considering the resting low blood pressure levels. As in conscious animals there was no tachycardia; if anything the heart rate was reduced.

Ketanserin was administered i.c.v. to conscious or anaesthetized SHR and SDR (25–50–100–500 μg, n = 3–11). Regardless of strain or level of consciousness cardiovascular changes were slight following the low doses. As can be seen from Table 1 administration of larger amounts had variable effects. Notably, only a very large dose, 500 μg, elicited significant hypotension in anaesthetized SHR.

In conscious SDR, spinalized and depleted of catecholamines, a single injection of 5-HT, 25 μg, caused a shortlasting pressor response followed by hypotension. The lowest dose tested of ketanserin, 0·16 mg kg^{-1}, completely inhibited the pressor responses but not the depressor response to 5-HT. In the same manner pressor responses to A and NA were antagonized significantly at 0·6 and 1·25 mg kg^{-1}, respectively. Even with large doses, e.g. 10 mg kg^{-1}, ketanserin affected neither the vasodepressor response nor the tachycardia to isoprenaline (Table 2).

DISCUSSION

The present study demonstrates that ketanserin in a dose range where it produces hypotension in the rat antagonizes pressor responses to A and NA. If this is indicative of an α-adrenoceptor interaction by ketanserin an α-adrenolytic action might contribute to the

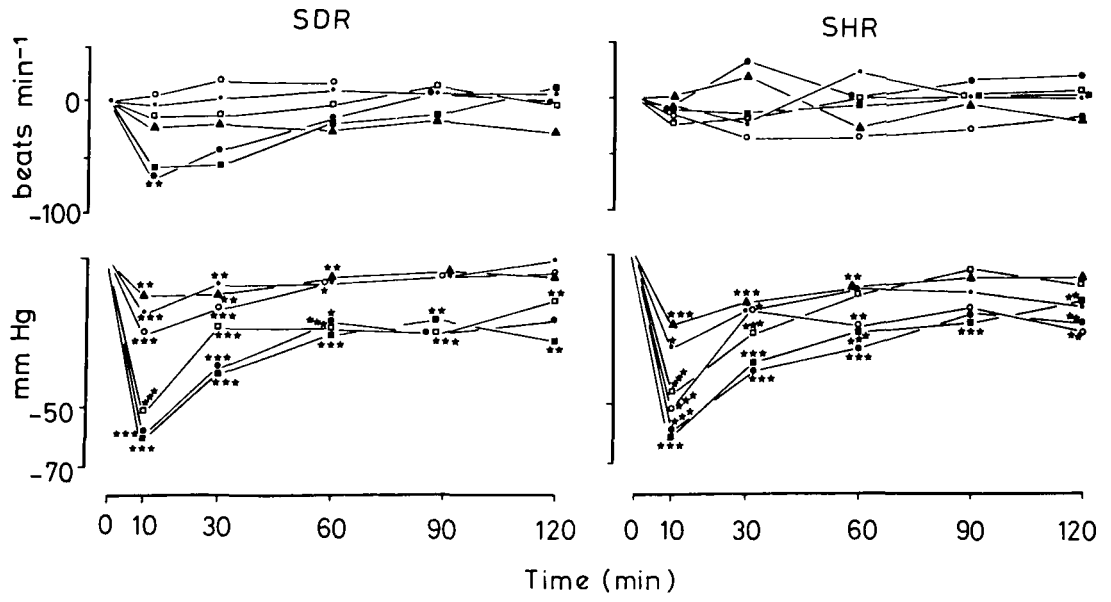

FIG. 1. Cardiovascular effects of i.v. ketanserin in conscious SDR (to the left) and SHR (to the right). The values are means of arterial blood pressure (mm Hg. lower ordinate) and heart rate (beats min^{-1}, upper ordinate) expressed as changes from basal levels. Basal levels are indicated within brackets as: b.p. mm Hg/HR beats min^{-1} with values for SDR given first. 3–10 rats in each group. ● 0 3 mg kg^{-1} (102/420, 141/437), ▲ 0·6 mg kg^{-1} (105/435, 129/417), □ 1·2 mg kg^{-1} (99/415, 136/410). ○ 2·5 mg kg^{-1} (110/400), ■ 5 mg kg^{-1} (113/420, 137/403), ● 10 mg kg^{-1} (112/325, 138/376). Asterisks indicate significances of differences from own basal level (calculated from absolute values). * $P < 0·05$, ** $P < 0·025$, *** $P < 0·005$.

Table 1. Mean arterial blood pressure (BP, mm Hg) and heart rate (HR, beats min^{-1}) with their s.e.m. after i.c.v. administration of ketanserin in conscious and anaesthetized SDR and SHR.

Doses (μg) of ketanserin and category		n	0 min (basal)		5 min		15 min		30 min		60 min	
			BP	HR	BP	HR	BP	HR	BP	HR	BP	HR
Conscious	SDR, 100 μg	3	117±6	390±26	102±7**	405±27	116±6	420±45	114±8	407±43	107±2	405±20
	500	5	113±6	325±15	129±7**	365±15	116±7	357±18	110±4	365±20	109±7	374±23
	SHR, 100	7	139±6	335±12	143±6	367±15	143±5	382±16**	143±5	379±21**	137±6	374±16**
	500	6	147±6	355±10	166±7***	423±21***	156±7	418±14***	154±6	380±8	144±5	394±12**
Anaesth.	SDR, 100	3	65±15	462±12	52±1	390±60	60±15	352±78	70±18	417±59		
	500	2	62±12	460±20	71±9	500±30	60±20	458±18	68±15	425±13		
	SHR, 100	4	102±5	409±16	94±11	415±25	89±5	365±8	78±7*	361±16	92±8	431±24
	500	10	106±3	421±8	81±8	356±15	83±8**	334±20	96±7	338±22	106±5	410±5

Asterisks denote differences from own basal level. * $P < 0.05$, ** $P < 0.025$, *** $P < 0.005$. n = number of experiments.

hypotension induced by this agent in acute experiments. Such a notion would be compatible with the finding that ketanserin at relatively moderate concentrations interacts with α-adrenoceptors in in vitro experiments, e.g. binding studies (Leysen et al 1981). Clearly, hypotension is not likely exclusively due to blockade of those 5-HT mechanisms mediating pressor responses to exogenous administration of 5-HT, since amongst other actions cyproheptadine, another 5-HT receptor blocking agent, inhibits those responses without inducing hypotension (Feniuk et al 1981; Antonaccio & Coté 1976). However, ketanserin might yet interact with some hitherto unidentified 5-HT-receptor mediating sensitization to catecholamines in the vascular wall (van Nueten et al 1981).

In contrast to most other agents that decrease blood pressure by an action on the vascular wall, the hypotension following ketanserin administration is not regularly accompanied by a compensatory tachycardia in rats as well as in man (de Cree et al 1981). Obviously, this cannot be explained by an interaction with cardiac β-receptors since ketanserin did not antagonize the tachycardia to isoprenaline in reserpine pretreated rats. In the light of binding data (Leysen et al 1981) an agonistic action of ketanserin on presynaptic α-adrenoreceptors on cardiac accelerator nerves is also unlikely. Considering the lack of tachycardia or bradycardia in conjunction with hypotension is a pattern displayed by centrally acting drugs such as clonidine (Kobinger 1978) or α-methyldopa (Henning 1975), a central mechanism of action of ketanserin would be conceivable. Indeed, such a mechanism of action has been reported for methysergide, another 5-HT receptor blocking agent (Antonaccio et al 1975) in dogs. However, in the present experiments ketanserin, unlike methysergide, following i.c.v. administration to SHR and SDR did not produce hypotension or bradycardia. Thus, as predicted from pharmacological studies ketanserin did not seem to have any significant central cardiovascular effects. Possibly, the explanation for lack of tachycardia to ketanserin administration is that the compound primarily acts on the venous side thus increasing venous capacitance.

Ketanserin reduced blood pressure in normotensive as well as hypertensive rats over a large dose range. Discrepancies with other studies in this respect, i.e. poor responses in normotensive animals (van Nueten et al 1981) probably reflect different routes of administration and different normotensive

Table 2. Maximal increase in blood pressure (mean ± s.e.m., mm Hg) and maximal decreases in heart rate (mean ± s.e.m., beats min^{-1}, only shown for Iso) to i.v. injections of NA (0·5 μg), A (0·5 μg), 5-HT (25 μg) and isoprenaline (0·025 μg) before and after various doses of ketanserin.

Dose of ketanserin mg kg^{-1}	Control				After ketanserin			
	NA	A	5-HT	Iso	NA	A	5-HT	Iso
0·16			52 ± 12				−8 ± 11*	
0·3		81 ± 8				76 ± 10		
0·6		81 ± 8				60 ± 3*		
1·25	85 ± 4	90 ± 23			61 ± 3**	13 ±12*		
10	86 ± 7	83 ± 4		−28 ± 4	50 ± 5*	2 ± 12*		−28 ± 2
				52 ± 17				42 ± 8

Basal levels did not differ significantly before and after ketanserin. One animal was used for one dose of ketanserin. The rats were pretreated with reserpine (10 mg kg^{-1} i.p., 6 h) and spinal transection (2 h). * $P < 0.05$, ** $P < 0.025$ (paired t-test). 4 animals were used for each dose.

rat strains. Apart from larger blood pressure reductions to lower doses of ketanserin in SHR there seemed to be no obvious differences between the strains tested. Obviously, in view of the likelihood of an α-adrenolytic component in the action of ketanserin no conclusion can be drawn from these experiments regarding the alleged vascular hypersensitivity to 5-HT in SHR (Collins & Vanhoutte 1981).

In summary, i.v. administration of ketanserin produces hypotension without a significant concomitant tachycardia in conscious or anaesthetized SDR and SHR. There were no indications for a central mechanism of action. Finally, ketanserin has α-adrenolytic actions at the same doses as those which lower blood pressure which suggest that its α_1-adrenoceptor blocking activity is involved in its hypotensive action in the rat. Whether these findings have any relevance to man remains to be determined, particularly when considering the notoriously large inter-species variation regarding 5-HT mechanisms and blood pressure control (see e.g. Kuhn et al 1980).

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