Kidney International, Vol. 38 (1990), pp. 823–829

Effect of a serotonin blocking agent on renal hemodynamics in the normal rat

NORBERT H. LAMEIRE, ERVE MATTHYS, DIRK KESTELOOT, and MARIE-ANNE WATERLOOS

Renal Division, Department of Medicine, University Hospital, Ghent, Belgium

Effect of a serotonin blocking agent on renal hemodynamics in the normal rat. These studies were designed to explore the effects of ketanserin (K), a serotonergic S2-receptor blocker on glomerular filtration rate (GFR), renal plasma flow (RPF) and autoregulation of renal blood flow (RBF) in the normal, anesthetized rat. Two doses of ketanserin were used: a high dose that, in addition to its serotonin blocking effect, possessed alpha1-adrenergic blocking capacities; and a low dose that acted only as a serotonin S2 blocking agent. The effects of the high dose were compared to the effects of phenotolamine. Both the high dose of K and phentolamine resulted in a similar fall of systemic blood pressure from 117 ± 4 to 78 ± 3 and from 121 ± 4.5 to 76 ± 5 mm Hg, respectively ($P < 0.01$). Despite this fall, GFR and RPF remained unchanged from 2.36 ± 0.16 ± to 2.26 ± 0.12 ml/min, and from 5.33 ± 0.41 to 5.76 ± 0.5 ml/min with K, while both parameters significantly decreased with phentolamine. A remarkable preservation of the autoregulation of RBF until a renal perfusion pressure (RPP) of 70 to 75 mm Hg was noted with K, but not with phentolamine or Ringer infusion. With the low dose of K, a significant rise in GFR and PAH clearance was noted, from 2.12 ± 0.17 to 2.59 ± 0.18 and from 4.81 ± 0.35 to 5.66 ± 0.48 ml/min, respectively ($P < 0.05$). A similar preservation of autoregulation of RBF was observed. Our studies suggest that in the pressure ranges below normal autoregulation of RBF in the rat, serotonin blockade is associated with maintenance of both GFR and RBF.

Serotonin or 5-hydroxytryptamine (5-HT) is a naturally occurring, biologically active amine that has the potential for affecting renal hemodynamics. The enteroendocrine (enterochromaffin) cells of the gastrointestinal wall contain the bulk of the serotonin in the body [1] and probably account for the majority of the serotonin reaching the blood. Recently, Sole et al [2] have described a very effective synthesis of serotonin in the proximal tubule of the rat kidney and in the non-blood perfused rat kidney. Their study revealed that it may be formed from its amino acid precursor, 5-hydroxytryptophan [3]. Moreover, in some disease states, serotonin is abundantly released from platelets [4].

Previous studies in the dog have shown divergent reactions of the renal vasculature to serotonin. Whereas some authors observed an increase in renal plasma flow in the anesthetized animal [5, 6], others reported a net decrease in renal blood flow [7, 8].

Received for publication November 27, 1989
and in revised form June 4, 1990
Accepted for publication June 5, 1990

Recently, Blackshear and coworkers described the presence of four components in the canine renal vascular response to serotonin, two leading to net vasodilatation, and two resulting in vasoconstriction [9]. In contrast with the dog, there is apparent consistency with which serotonin induces renal vasoconstriction in the rat [10–13]. Based on radioligand studies in animals, two different forms of 5-HT-receptors have been defined [14]. The vascular effects of serotonin are complex, but contraction of the vascular smooth muscle is, among others, thought to be the consequence of activation of $5HT_2$- or S_2-serotonergic receptors [15, 16].

The development of ketanserin, a selective S_2 serotonergic antagonist, and devoid of agonistic serotonergic properties [16], has clarified many of serotonin's vascular reactions. Ketanserin is effective in curtailing the direct and indirect vasoconstrictor properties of serotonin but does not seem to interfere with the vasodilatation that 5-HT can cause [17].

However, ketanserin possesses also alpha 1-adrenergic blocking properties which, although they occur at higher concentrations than required to block S_2-serotonergic receptors, may at least contribute to its, well-established antihypertensive effect [18, 19]. The present study reports the acute effects of ketanserin on renal function and renal blood flow in the normal anesthetized rat, to elucidate a possible role of serotonin in the mechanism of renal blood flow autoregulation.

Two doses of ketanserin were used to differentiate the alpha 1-adrenergic from the serotonergic S_2-antagonistic effects. The effects of the alpha-adrenergic blocking dose were compared with those of phentolamine.

Methods

All studies were performed in male Wistar rats, weighing 280 to 335 g which were deprived of food but allowed free access to water overnight prior to study. The animals were anesthetized with sodium pentobarbital (50 mg/kg i.p.) and placed on a heating table that maintained normal body temperature.

A tracheostomy was performed, and one carotid artery and one jugular and femoral vein were cannulated. Femoral arterial blood pressure was monitored throughout the experiment with a Statham transducer connected to a Beckman Dymograph. When clearance studies were performed, a small midline abdominal incision was made to expose both urethers which were catheterized with a PE50 catheter.

In the experiments where renal blood flow was measured, a small flow transducer connected to a square wave electromag-

netic flowmeter (EMF; Skalar Medical, Delft, The Netherlands) was placed around the right renal artery, near its origin at the aorta.

The flowmeter system was calibrated in vitro periodically throughout the study. This consisted of constant infusions of heparinized rat blood, at known rates, through a cannulated excised segment of a rat carotid artery. Absolute zero flow through the renal artery was determined on several occasions during the experiment by completely occluding the artery distal to the probe with a forceps for two to three seconds; baseline drift was negligible.

For injection of drugs into the right renal artery, the technique of catheter implantation into the right suprarenal artery was used, as described by Smits et al [20]. Briefly, the suprarenal artery was carefully freed from connective tissue and small ligatures were passed under the vessel. Cannulation of the artery was performed by means of catheters constructed of a 15 cm piece of PE_{10} tubing, also described by Smits et al [20]. The catheters had an outer diameter of approximately 0.2 mm and an inner diameter of 0.1 mm. After stabilization of renal blood flow for at least 30 minutes, drugs were injected via the suprarenal artery and renal blood flow response was monitored with the EMF meter.

Dose finding studies of ketanserin and dose response curves

In these studies, bolus injections of phenylephrine ($N = 5$) and serotonin (Sigma Chemical Company, St. Louis, Missouri, USA) ($N = 6$), were delivered into the right renal artery, while renal blood flow was continuously measured. The doses of phenylephrine were 0.1, 0.3, 0.5 and 1 μg and of serotonin were 0.3, 0.5, 1.0 and 2 μg. Either ketanserin (Janssen Pharmaceutica, Beerse, Belgium), phentolamine (Ciba, Basel, Switzerland) or Ringer solution were infused intravenously via the jugular vein. Pilot studies had shown that a bolus of 0.75 mg/kg ketanserin, followed by a 2 mg/kg hour continuous infusion was a dose which consistently produced a fall in systemic blood pressure between 75 and 80 mg Hg. To achieve the same blood pressure reduction, an intravenous bolus of phentolamine 0.35 mg/kg, followed by a continuous infusion of 1 mg/kg hour was necessary.

A much lower dose of ketanserin in an i.v. bolus of 0.05 mg/kg, followed by an i.v. infusion of 0.1 mg/kg hour was also utilized. This dose was devoid of alpha blocking effects but completely blocked the renal hemodynamic response to intrarenal serotonin.

Clearance studies

An isotonic Ringer solution containing 10% inulin and 1.7% para-amino hippuric acid (PAH) was, after a small bolus injection, infused intravenously at a rate of 0.05 ml/min throughout the course of the experiment. An equilibration period of 60 minutes was allowed prior to three, 10-minute control clearance collections.

Four groups of clearance studies were performed.

Group a: High dose ketanserin (N = 14). After termination of the control collections, the high dose of ketanserin was intravenously administered. After stabilization of the systemic blood pressure around 75 to 80 mm Hg for at least 25 to 30 minutes, three experimental (10 min) clearance collections were obtained. After termination of these collections, the ketanserin infusion was stopped, and after returning of the blood pressure to a stable value for at least 20 to 25 minutes, three additional clearance collections were performed.

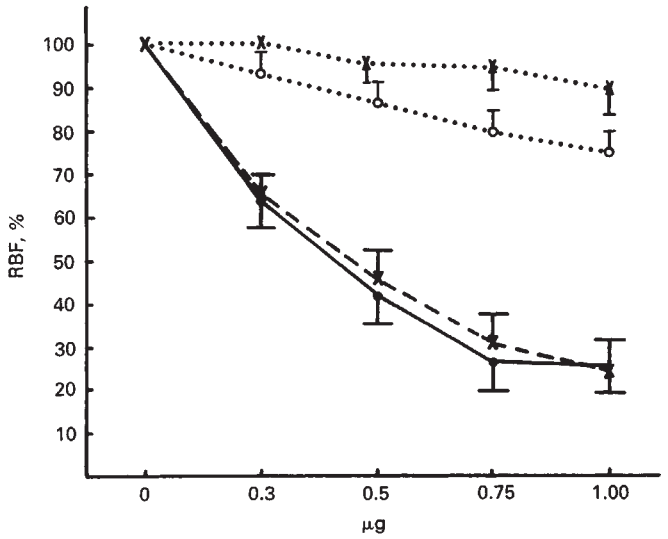

Fig. 1. *Percent changes in renal blood flow to increasing doses of intrarenal phenylephrine.* Symbols are: (closed circles) phenylephrine alone; (Open circles) during high dose of ketanserin; (crosses and interrupted line) during low dose of ketanserin; (crosses and solid line) during phentolamine. The values obtained with phenylephine alone and the low dose of ketanserin were not significantly different from each other. The values obtained with phentolamine and the high dose of ketanserin were significantly different from each other at 0.5 ($P < 0.05$), 0.75 and 1 μg ($P < 0.01$) of the doses of phenylephrine.

Group b: Low dose ketanserin (N = 8). In these animals the same protocol was followed but a low dose of ketanserin was infused.

Group c: Phentolamine (N = 8). In these animals, phentolamine was infused. These animals served as controls for the experiments of group a, since the blood pressure achieved during the phentolamine infusion was comparable with the values obtained with the high dose of ketanserin (75 to 80 mm Hg).

Group d: Ringer's solution (N = 12). These animals were infused with a Ringer solution during the experimental clearance collections at the same rate as in the preceding groups of animals.

In all clearance studies, urine samples were collected in preweighed vials and the urine volume was gravimetrically determined. Blood samples were collected from the carotid artery at the beginning and the end of each clearance collection period for determination of inulin, PAH, sodium and hematocrit. The clearance results presented are the mean of three such 10 minute collections. Plasma and urine inulin and PAH concentrations were determined by the anthrone method [21] and by the method of Harvey and Brothers [22], respectively. The sodium concentrations in urine and plasma were measured with a Klina flame photometer (Beckman Instruments).

Autoregulation studies of renal blood flow

To obtain the autoregulation curves, a suture was placed around the aorta above both renal arteries. A short piece of PE10 tubing was slipped over the suture. The tubing was then

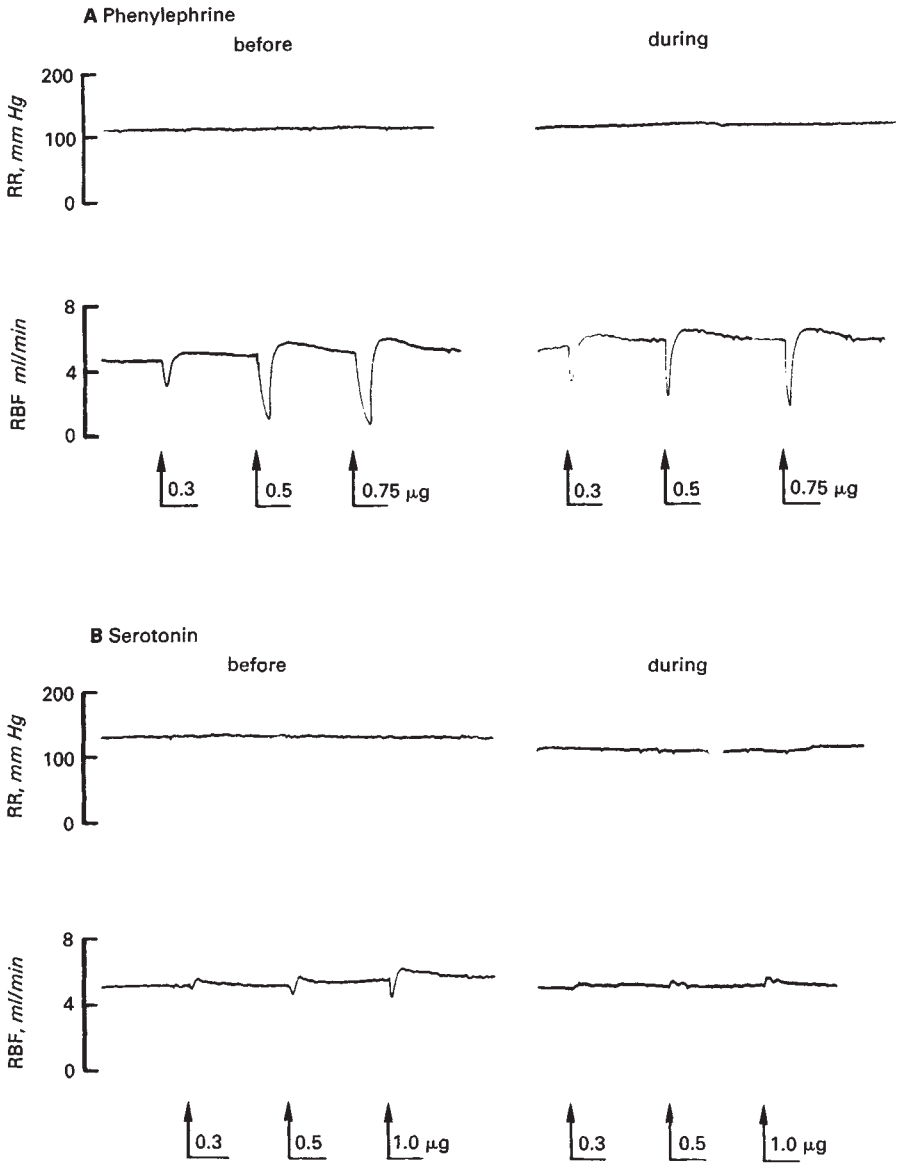

Fig. 2. *Tracing of blood pressure and renal blood flow response to intrarenal doses of phenylephrine (A) and of serotonin (B) before and during the infusion of the low dose of ketanserin.*

gradually compressed against the aorta for regulation of the renal perfusion pressure (RPP). To measure the latter, a catheter was threaded via the iliac artery into the aorta just below the level of the renal arteries. Renal perfusion pressure was equated with the blood pressure measured at this level. Renal blood flow (RBF) was monitored with the electromagnetic flow meter, as described above. The RPP was then gradually reduced by steps of 5 mm Hg down to 60 mm Hg. After three to five minutes of equilibration of RBF at each pressure level, RBF was recorded.

Autoregulation curves were obtained before, during and after administration of either the high ($N = 8$) or low ($N = 7$) dose ketanserin, phentolamine ($N = 7$), or Ringer's infusion ($N = 7$), strictly following the protocol of the clearance studies, as outlined above.

All data were analyzed by the Wilcoxon test for paired and unpaired observations. The results are presented as the mean ± standard error of mean. A P value less than 0.05 was considered to be significant.

Results

Dose-response curves

Figure 1 represents the percent changes in renal blood flow to increasing doses of intrarenal phenylephrine before and during the systemic administration of both doses of ketanserin and of phentolamine. It is clear that the vasoconstrictive response following phenylephrine is completely blocked by phentolamine and strongly attenuated by the high dose of ketanserin. During infusion of the low dose of ketanserin, however, a normal vasoconstrictive response to phenylephrine was obtained. Figure 2 depicts the tracing of the RBF response to intrarenal administration of increasing doses of phenylephrine and serotonin before and during the low dose of ketanserin. Figure 3

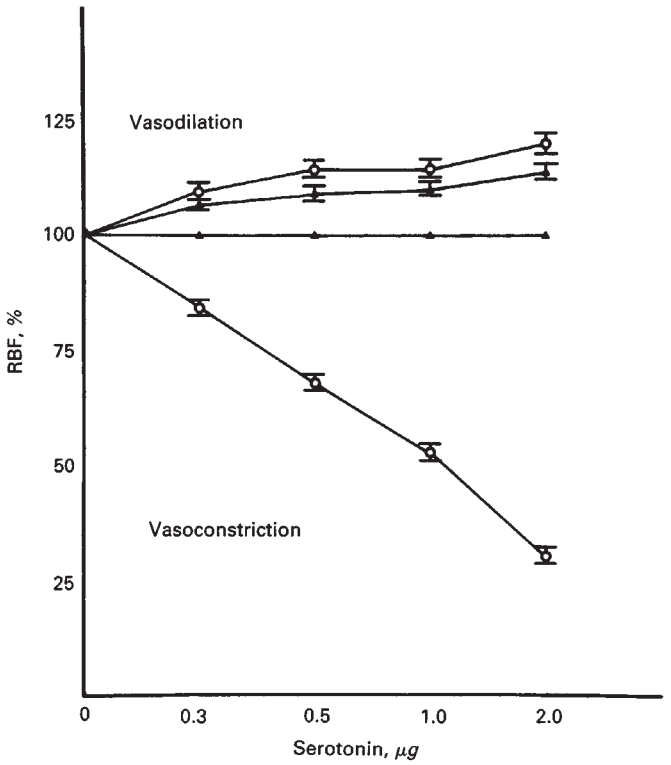

Fig. 3. *Dose-response relationship for renal blood flow when serotonin was injected into the renal artery.* Note the biphasic response, a first dose-related vasoconstriction, followed by vasodilatation. Symbols are: (open circles) before ketanserin; (triangles) during ketanserin. The changes with serotonin and ketanserin during the vasodilatation were not different from each other.

summarizes the results obtained in six animals with intrarenal serotonin during the low dose of ketanserin. A bolus injection of serotonin resulted in a biphasic response of RBF: first a pronounced vasoconstriction, followed by a smaller but significant vasodilation. Whereas it was clear that the vasoconstrictive response to serotonin was dose-dependent, the increment in RBF was clearly not dose-dependent.

It also appears that during the systemic infusion of the low dose of ketanserin, the vasoconstrictive response to serotonin was completely blocked. However, the secondary vasodilation was not affected during ketanserin.

Infusion of the high dose of ketanserin not only blocked the vasoconstriction following phenylephrine but also of serotonin (results not shown).

The results indicate that with the high dose, ketanserin was acting not only as a serotonin S_2, but also as an alpha 1-adrenergic receptor blocker. The low dose of ketanserin was devoid of alpha 1-blocking properties and can be considered as a serotonin S_2-receptor blocker on the renal circulation.

Clearance studies

The effects of both doses of ketanserin, phentolamine and Ringer's solutions on glomerular filtration rate (GFR), PAH clearance and fractional urinary extraction of sodium (FE_{Na}) and arterial blood pressure (BP) are shown in Table 1.

Despite a marked reduction in BP from 117 ± 3.9 to 78 ± 3 mm Hg during the high-dose ketanserin infusion, both GFR and PAH clearance remained unchanged (2.36 ± 0.16 vs. 2.26 ± 0.12 ml/min, and 5.33 ± 0.41 vs. 5.96 ± 0.48 ml/min; $P > 0.05$). After withdrawal of the drug, BP did not return completely towards control and remained at 93 ± 4.9 mm Hg. However, GFR and PAH clearance remained unchanged. FE_{Na} did not change significantly over the three collection periods. With the low dose of ketanserin, systemic blood pressure dropped significantly from 118 ± 4 to a mean of 104 ± 5 mm Hg ($P < 0.05$). However, this fall in BP was significantly less than with the high dose. A significant increase in GFR of 22% and in PAH clearance of 18% was observed. The FE_{Na} did not change.

During phentolamine infusion, a similar fall in BP from 121 ± 4.5 to 76 ± 5.0 mm Hg was noted as with the high dose of ketanserin. However, a significant fall in both GFR from 1.98 ± 0.09 to 1.28 ± 0.17 ml/min ($P < 0.01$) and in PAH clearance from 4.80 ± 0.32 to 3.54 ± 0.4 ml/min ($P < 0.05$) was observed.

After withdrawal of the phentolamine, BP returned to 98 ± 7 mm Hg and both GFR and PAH clearance increased in comparison to the control values without, however, showing complete recovery. With Ringer's solution, no significant changes in any of the studied renal functional parameters occurred.

No consistent changes in FE_{Na}, nor in Hct (not shown) were noted in all groups.

Autoregulation studies

Figure 4 summarizes the percent of changes in RBF to variations in renal perfusion pressure with the high dose of ketanserin (A) and phentolamine (B) before, during and after the infusion of the drugs.

Before ketanserin the mean RBF of 4.92 ± 0.31 ml/min remained stable when RPP ranged from 120 to 95 mm Hg. Below this range, RBF decreased progressively from 98% of control flow at 95 mm Hg to 71% at 60 mm Hg. During ketanserin, the RPP before starting the autoregulation study had fallen to a mean of 80 ± 2 mm Hg, corresponding with a RBF value of 4.35 ± 0.21 ml/min. Further and gradual lowering of the RPP from 80 to 50 mm Hg revealed an efficient autoregulation of RBF until an RPP of 65 mm Hg. RBF at this pressure was still 90% of the control value, but decreased to 68% of control at a RPP of 50 mm Hg.

After the high dose of ketanserin infusion, the autoregulation curve was very similar to the one obtained before the infusion.

The control RBF in the animals infused with phentolamine was 5.20 ± 0.27 ml/min, and decreased significantly with 30% to 3.50 ± 0.31 ml/min at a blood pressure of 80 mm Hg with phentolamine ($P < 0.05$), and before the autoregulation study had begun.

Whereas a normal autoregulation was obtained before phentolamine, during the infusion with pentolamine, RBF was not longer maintained when RPP was further reduced. At 75 mm Hg, RBF was only 75% of the control value, which is in sharp contrast with the 90% at the same RPP during ketanserin ($P < 0.001$). After phentolamine, autoregulation was again normal with a reduction of only 5% of the control value at an RPP of 90 mm Hg.

Figure 5 shows the percent changes in RBF to lowering the RPP before and during the infusion of the low dose of ketan-

Table 1. Effects of ketanserin, phentolamine, and ringer's solution on renal function

	GFR *ml/min*			PAH clearance *ml/min*			Fractional excretion of sodium *%*			Systemic BP *mm Hg*		
	Before	During	After	Before	During	After	Before	During	After	Before	During	After
Ketanserin												
High dose	2.36	2.26	2.42	5.33	5.76	5.66	0.12	0.11	0.15	117	78	93
(N = 14)	±0.16	±0.12	±0.17	±0.41	±0.5	±0.43	±0.02	±0.01	±0.03	±4	±3[a]	±5[b]
Low dose	2.12	2.59	2.31	4.81	5.66	5.12	0.11	0.18	0.17	118	104	106
(N = 8)	±0.17	±0.18[a]	±0.26[b]	±0.35	±0.48[a]	±0.6	±0.01	±0.02[b]	±0.04	±4	±5[b]	±6
Phentolamine	1.98	1.28	1.55	4.80	3.54	4.43	0.14	0.22	0.19	121	76	98
(N = 8)	±0.09	±0.17[a]	±0.17[b]	±0.32	±0.4[b]	±0.3	±0.09	±0.4[b]	±0.4	±4.5	±5[a]	±7[a]
Ringer's	2.16	2.20	2.13	4.90	5.18	5.29	0.08	0.12	0.16	116	117	113
(N = 7)	±0.34	±0.32	±0.27	±0.37	±0.67	±1.0	±0.01	±0.01	±0.07	±0.12	±12	±11

[a] $P < 0.01$ from results before ketanserin or phentolamine
[b] $P < 0.05$ from results before ketanserin or phentolamine

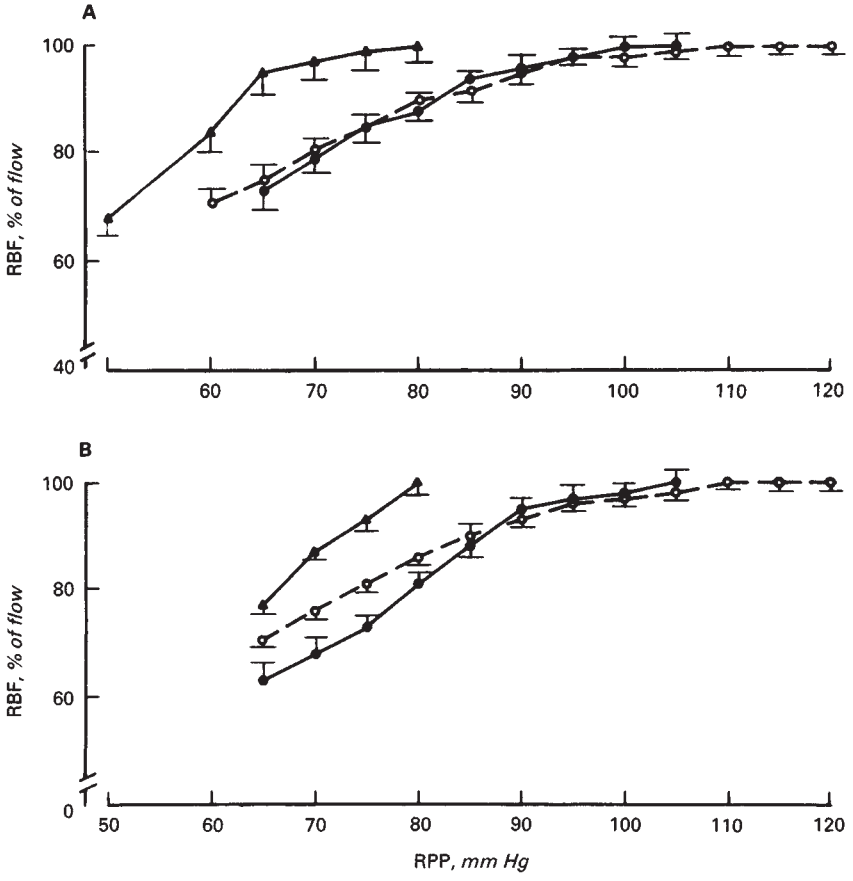

Fig. 4. *Percent changes in renal blood flow to reductions in renal perfusion pressure.* Effect of high dose of ketanserin (**A**) and of phentolamine (**B**). Symbols are: (○) before; (▲) during; (●) after.

serin. With ketanserin, a slight drop in basal mean systemic blood pressure from 125 to 105 mm Hg was observed. Before ketanserin, a normal autoregulation curve was obtained with a deflection point between 90 and 95 mm Hg. During the ketanserin infusion, basal RBF in the right kidney was increased from 5.17 ± 0.65 ml/min to 5.71 ± 0.52 ml/min ($P < 0.05$) at normal RPP. Adequate autoregulation was maintained until a RPP of 75 mm Hg. At this level RBF was still 90% of its initial value.

At a RPP of 65 mm Hg, RBF was 85% of the control value, which is significantly higher than the 62% obtained at the same pressure level before ketanserin. In these experiments no autoregulation studies were performed after stopping the drug infusion. The basal value of RBF in the experiments before the Ringer infusion was 5.45 ± 0.28 ml/min.

Before, during and 60 minutes after stopping the Ringer's infusion, autoregulation curves were normal and not different from the pre-drug control curves in the ketanserin or phentolamine experiments. (results not shown).

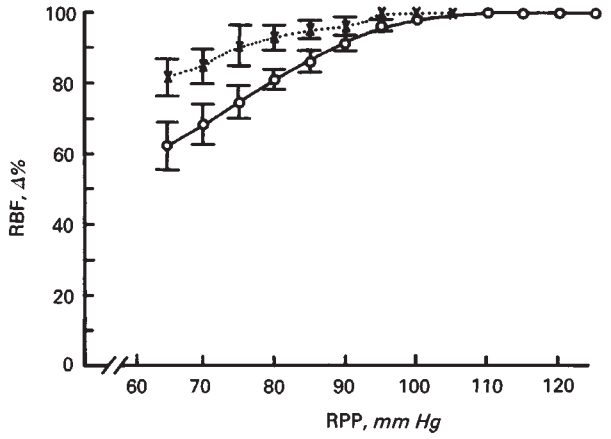

Fig. 5. *Percent changes in renal blood flow to reduction in renal perfusion pressure before (open circles) and during (crosses) low doses of ketanserin.*

Discussion

The main purpose of this study was to investigate the acute effects on renal function and autoregulation of RBF of ketanserin, a known antagonist of serotonin S_2 receptors. It is, however, well established and also confirmed by our study, that depending on the dose, ketanserin possesses alpha-receptor blocking effects. In fact, the fall in blood pressure noted in numerous clinical studies has at least partly been ascribed to its alpha blocking characteristics and cannot be fully explained by its serotonin-antagonistic effects [18, 19].

Our experiments with the high dose of ketanserin were designed to study the effects of ketanserin on renal function in presence of a consistent fall in blood pressure below the autoregulation range of RBF in the rat. Based on the dose response curves to phenylephrine, it is without doubt that ketanserin was acting mainly as an alpha blocking agent. Therefore, separate studies with phentolamine, a pure alpha blocking agent were performed in an attempt to discern differences in renal effects between the two drugs.

It is remarkable to note (Table 1) that with the high dose of ketanserin and despite the fact that blood pressure, and presumably the renal perfusion pressure, was lowered to 78 mm Hg, GFR, PAH clearance and renal blood flow were preserved. This was in contrast with the findings observed with phentolamine, where—as expected—a fall in GFR, PAH clearance and RBF was seen when the BP was decreased to the same level.

Previous studies have shown, and this study confirms, that in the rat, RBF is well autoregulated until a RPP between 90 and 95 mm Hg [23, 24]. This is in contrast with autoregulation of RBF in other species, for example in the dog, where RBF is maintained constantly when RPP is lowered to approximately 80 mm Hg [25–27].

Since not only RBF but also GFR is autoregulated over approximately the same pressure range, it was interesting to investigate the autoregulatory capacity of RBF below the normal autoregulatory pressure range in the rat. A remarkably preserved efficiency for autoregulation of RBF with the high dose of ketanserin, but not with phentolamine was observed. This leads to the conclusion that both agents, while exerting an alpha-blocking effect have different effects on the renal hemodynamics. It was therefore inevitable to conclude that this difference was due to the serotonin antagonism during the ketanserin-infusion.

Consequently, the studies were repeated with a low dose of ketanserin which was devoid of alpha 1-blocking effects and for which it was established that it acted via an S_2-antiserotonergic mechanism. The same results on autoregulation of RBF with this low dose of ketanserin were obtained.

Furthermore, GFR, PAH clearance and RBF, the latter directly measured with the electromagnetic flowmeter, increased approximately 20 percent with this low dose of ketanserin.

That the maintenance of RBF below the normal autoregulatory range of renal perfusion pressure with ketanserin is real is confirmed by two additional findings. First, there is no "shift" in the autoregulatory range with time as indicated by our results obtained with the Ringer's solution. Second, we recently completed studies in our laboratory showing that the low dose of ketanserin was able to restore the normal autoregulatory capacity of the renal vascular bed in a model of post-ischemic acute renal failure where autoregulation of RBF was lost, at 48 hours and one week post-reperfusion [28]. It is tempting to speculate on the mechanism by which an anti-serotonergic agent is able to exert these hemodynamic effects. It is accepted that during autoregulation of RBF in presence of a lowering perfusion pressure the intrarenal vascular resistance progressively falls until the lowest renal perfusion pressure where RBF is perfectly maintained [23, 24]. This point corresponds with the deflection point of the autoregulation curve. Below this point intrarenal vascular resistance does not decrease further, and in fact has a tendency to rise again when renal perfusion pressure is further lowered [24, 25].

Serotonin is a known renal vasoconstrictor, acting via its S_2-serotonergic vascular receptors [10–12]. As shown also by our results, ketanserin effectively blocks this S_2-serotonergic vasoconstrictive mechanism without affecting the secondary vasodilatory effect.

It is also known that serotonin can be formed intrarenally by at least two pathways: the first via platelet aggregation in the blood perfused kidney; the second via decarboxylation of its amino acid precursor, L5-hydroxytryptophan (L-5-HTP) [2, 3].

A recent paper [29] has explored the renal effects of carbidopa, which blocks the peripheral conversion of 5.HTP to serotonin. The renal vasoconstriction to 5.HTP was completely abolished after carbidopa. That study therefore indirectly confirms the present results. As far as we know, the effect of carbidopa on autoregulation of RBF has not yet been studied.

It is conceivable that by lowering the renal perfusion pressure below the autoregulatory range, the serotonin formed contributes to the intrarenal vasoconstriction. This vasoconstriction is effectively blocked by ketanserin. To our knowledge, a role for serotonin in the autoregulation of renal blood flow has not yet been investigated. It was not the purpose of our experiments to explore the efferent mechanisms of the intrarenal vascular adjustments during autoregulation. Two main mechanisms are thought to mediate these adjustements: either a primary myogenic response or the participation of a rapidly acting tubulovascular feedback at the individual nephron level [30].

Whatever theory has been proposed to explain RBF autoregulation, this phenomenon is basically an intrinsic vascular

function mainly at the preglomerular sites that governs the adaptation of the vasculature to changes in perfusion pressure [30].

The exact cellular mechanisms responsible for transmitting the signals to the glomerular arterioles, however, remain poorly understood. Our studies suggest that in the regulation of renal blood flow, at least in the pressure ranges below normal autoregulation, serotonin may play an important role.

Acknowledgments

This research was supported by a grant from the Nationaal Fonds voor Wetenschappelijk Geneeskundig Onderzoek (NFWGO). Ketanserin used in this study was generously supplied by Janssen Pharmaceutica. The authors are grateful to Drs. Struyker-Boudier and Smits from the University of Maastricht, the Netherlands, for demonstrating the technique of suprarenal artery catheterization. The secretarial expertise from C. Bergen, K. Verlinde and M. Gillis is much appreciated.

Reprint requests to N. Lameire, Renal Division, Department of Medicine, University Hospital, De Pintelaan 185, B-9000 Ghent, Belgium.

References

1. ERSPAMER V: Quantitative estimation of 5-HT in gastrointestinal tract, spleen and blood of vertebrates, in *Ciba Symposium on Hypertension*, edited by B WOLSTENHOLME, MP CAMERON, London, Churchill, 1954, pp 78–84
2. SOLE MJ, MADAPALLI MATTAM A, BAINES AD: An active pathway for serotonin synthesis by renal proximal tubules. *Kidney Int* 29:689–694, 1986
3. STIER CT JR, MC KENDALL G, ITSKOVITZ HD: Serotonin formation in non blood-perfused rat kidneys. *J Pharmacol Exp Ther* 228:53–56, 1984
4. HELLER J: Effect of vasoactive mediators on renal haemodynamics. *Nephrol Dial Transplant* 2:197–204, 1987
5. SPINAZZOLA AJ, SHERROD TR: The effect of serotonin (5-hydroxytryptamine) on renal hemodynamics. *J Pharmacol Exp Ther* 119: 114–121, 1957
6. MC CUBBIN JW, KANEKO Y, PAGE IH: Inhibition of neurogenic vasoconstriction by serotonin. *Circ Res* 11:74–83, 1962
7. ERSPAMER V: Pharmacological studies on enteramine (5-hydroxytryptamine). Influence of sympathicomimetic and sympatholytic drugs on the physiological and pharmacological actions of enteramine. *Arch Int Pharmacodyn Ther* 93:293–316, 1953
8. EMANUEL DA, SCOTT J, COLLINS R, HADDY FJ: Local effect of serotonin on renal vascular resistance and urine flow rate. *Am J Physiol* 196:1122–1126, 1959
9. BLACKSHEAR JL, ORLANDI C, HOLLENBERG NK: Serotonin and the renal blood supply: Role of prostaglandins and the $5HT_2$ receptor. *Kidney Int* 30:304–310, 1986
10. PAGE E, GLENDENNING M: Production of renal cortical necrosis with serotonin (5-hydroxytryptamine). *Am J Med* 19:285–286, 1955
11. HYSELL J, BOHR D: Renal vascular responses to plasma and to known vasoactive substances. *Proc Soc Exp Biol Med* 135:930–953, 1970
12. CERLETTI A, CAPRI A, ROTHLIN E: Uber die Wirkung von 5-oxytryptamin (Serotonin) auf Diurese und Nierendurchblutung. *Helv Physiol Acta* 13:C8–C9, 1955
13. DEL GRECO F, MASSON G, CORCORAN A: Renal and arterial effects of serotonin in the anesthetized rat. *Am J Physiol* 187:509–514, 1956
14. PEROUTKA SJ, SNYDER S: Multiple serotonin receptors: Differential binding of (^{3}H)5-hydroxytryptamine, (^{3}H) lysergic acid diethylamide and (^{3}H) spiroperidol. *Molec Pharmacol* 16:687–699, 1979
15. VANHOUTTE PM, LÜSCHER TF: Serotonin and the blood vessel wall. *J Hypertension* 4(Suppl 1):S29–S35, 1986
16. VAN NUETEN JM, JANSSEN PAJ, VAN BEEK J, XHONNEUX R, VERBEUREN TJ, VANHOUTTE PM: Vascular effects of ketanserin (R41468), a novel antagonist of $5\text{-}HT_2$ serotonergic receptors. *J Pharmacol Exp Ther* 218:217–230, 1981
17. COHEN RA, SHEPHERD JT, VANHOUTTE PM: 5-hydroxytryptamin can mediate endothelium-dependent relaxation of coronary arteries. *Am J Physiol* 245 (Heart Circ Physiol 14):H1077–H1080, 1983
18. FOZARD JR: Mechanism of the hypotensive effect of ketanserin. *J Cardiovasc Pharmacol* 4:829–838, 1982
19. RICHER C, SCALBERT E, DOUSSEAU MP, DUHAZE P, GINDICELLI JF: Ketanserin: Systemic and regional hemodynamics in spontaneously hypertensive rats. Role of alpha 1-adrenoceptor blockade. *Eur J Pharmacol* 139:31–42, 1987
20. SMITS JFM, KASBERGEN CM, VAN ESSEN H, KLEINJANS JC, STRUYKER BOUDIER HAJ: Chronic local infusion into the renal artery of unrestrained rats. *Am J Physiol* 244:H304–H307, 1983
21. FÜHR J, KACZMARCZYK J, KRÜTTGEN CD: Eine einfache Colorimetrische Methode zum Inulinbestimmung für Nierenclearance-Untersuchungen bei stoffwechselgesunden und Diabetikern. *Klin Wochenschr* 33:729–730, 1955
22. HARVEY RB, BROTHERS AJ: Renal extraction of para-aminohippurate and creatinine measured by continuous in vivo sampling of arterial and renal vein blood. *Ann NY Acad Sci* 102:46–50, 1962
23. ARENDSHORST WJ, FINN WF, GOTTSCHALK CW: Autoregulation of blood flow in the rat kidney. *Am J Physiol* 228:127–133, 1975
24. ARENDHORST WJ: Autoregulation of renal blood flow in spontaneously hypertensive rats. *Circ Res* 44:344–349, 1979
25. SELKHURST EE, HALL PW, SPENGER MP: Influence of graded arterial pressure decrements on renal clearance of creatinine, p-aminohippurate and sodium. *Am J Physiol* 159:369–378, 1949
26. SHIPLEY RE, STUDY RS: Changes in renal blood flow, extraction of inulin, glomerular filtration rate, tissue pressure and urine flow with acute alterations of renal artery blood pressure. *Am J Physiol* 167:676–688, 1951
27. THURAU K, WOBER E: Zur Lokalisation der Autoregulation Widerstandsänderungen in der Niere. *Arch Ges Physiol* 274:553–566, 1962
28. SMÖLLICH BP, KESTELOOT D, LAMEIRE N: Studies on autoregulation of renal blood flow in the ischemic rat kidney. (abstract) *XXVI Congress of the European Dialysis and Transplant Association*, 1989, p. 9
29. DING XR, STIER CT, ITSKOVITZ HD: Serotonin and 5-hydroxytryptophan on blood pressure and renal blood flow in anesthesized rats. *Am J Med Sci* 297:290–293, 1989
30. ARENDSHORST WJ, NAVAR LG: Renal circulation and glomerular hemodynamics, in *Diseases of the Kidney*, edited by RW SCHRIER, CW GOTTSCHALK, Boston, Little, Brown and Co, 1988, pp. 65–117