Kidney International, Vol. 30 (1986), pp. 304–310

Serotonin and the renal blood supply: Role of prostaglandins and the 5HT-2 receptor

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Serotonin and the renal blood supply: role of prostaglandins and the 5HT-2 receptor. Serotonin (5HT) has been reported to increase, to decrease, or not to change renal blood flow. We postulated that prostaglandin release in response to 5HT acted as a confusing variable, and tested the hypothesis by comparing infusions of serotonin and angiotensin into one renal artery of 14 anesthetized dogs before and after indomethacin administration. Renal blood flow (Q, by EM flowmeter) responses to 5HT were routinely biphasic, an initial sharp decrease followed by a gradual increase which stabilized well above baseline at three to six minutes. Indomethacin, 1 to 2 mg/kg, did not alter the acute Q decrement induced by 5HT but abolished the increase in Q at three to six minutes ($P < 0.001$). Instead, sustained vasoconstriction became apparent. Ketanserin reversed the sustained vasoconstrictor effect of 5HT in indomethacin–treated dogs, leading to striking, serotonin–induced vasodilatation. The latter vasodilatation in turn was inhibited by methysergide. Four independent elements, two promoting vasoconstriction and two vasodilatation, are suggested. One vasodilator response is abolished by prostaglandin synthetase inhibition and the other by methysergide, a complex 5HT receptor blocker. The sustained vasoconstrictor response is blocked by ketanserin, suggesting an action on the 5HT-2 receptor. The initial, transient vasoconstrictor response is resistant to the blockers employed. These complex interactions may account for the variability in reported responses of the renal blood supply to serotonin.

There has been substantial interest in the renal action of serotonin in the several decades since its discovery, but no clear indication as to its action within the kidney, or its role in pathogenesis [1]. In part the difficulty in defining its role has reflected the wide variation in reports on both the direction and magnitude of the renal vascular response, some investigators reporting a net increase in renal blood flow [2, 3], whereas others reported vasoconstriction [4–6], or no change despite the use of substantial doses [7–9]. The recognition that local prostaglandin release modulates the renal vascular response to vasoconstrictor hormones such as norepinephrine and angiotensin [10, 11] led to one working premise in this study.

The development of a 5HT-2 receptor antagonist has clarified many of serotonin's vascular actions: where serotonin induces vasoconstriction, the response has been blocked by ketanserin, the 5HT-2 antagonist [12–16]. This response differs from that seen with serotonin antagonists available hitherto, which lack selectivity for the 5HT-2 receptor and often have partial agonist action.

In this study we describe four components in the canine renal vascular response to serotonin, two leading to net vasodilatation, and two resulting in vasoconstriction. Vasodilator effects were sensitive to indomethacin and methysergide, but not to ketanserin, while the dominant constrictor mechanism, evident only after prostaglandin synthetase inhibition, is reversed by ketanserin, the 5HT-2 antagonist.

Methods

Studies were performed on 14 mongrel dogs. They were anesthetized with sodium pentobarbital, 30 mg/kg i.v., the trachea was intubated and ventilation was supported. Each dog received one liter of normal saline i.v. in the hour after induction to replace losses due to surgery. Animals used in this study were maintained in accordance with the guidelines of the Committee on Animals of the Harvard Medical School and those prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council.

Pressure and flow measurements

A 5 to 5.6 French polyethylene catheter was placed in a superficial femoral artery and was directed to a selective renal arterial position under fluoroscopic guidance. Through a flank incision, a 3.0 to 3.5 mm diameter electromagnetic flow probe connected to a SP2202 Statham–Gould Flowmeter (Statham Instruments, Oxnard, California, USA) was placed on a renal artery for measurement of mean and phasic blood flow. Test injections of the contrast medium, meglumine diatrazoate, 60% were used to document proper position of the catheter tip relative to the flow probe. The catheter was kept open with a constant infusion of normal saline, 2.5 ml/min delivered by a Holter RD074 pump. Delivery of test injections and infusions were superimposed into this line to minimize injection artifacts on the flow tracing. Mean arterial pressure was monitored using a Statham P23DP pressure transducer connected to a Cordis arterial sheath (Cordis Dow Corp., Miami, Florida, USA) in the femoral artery. Pressures and flows were recorded continuously on a Grass Polygraph.

Protocols

Renal action of 5HT. Dose response relationships for intrarenal injections or infusions of 5HT were defined in eight dogs.

Received for publication August 31, 1984
and in revised form August 22, 1985

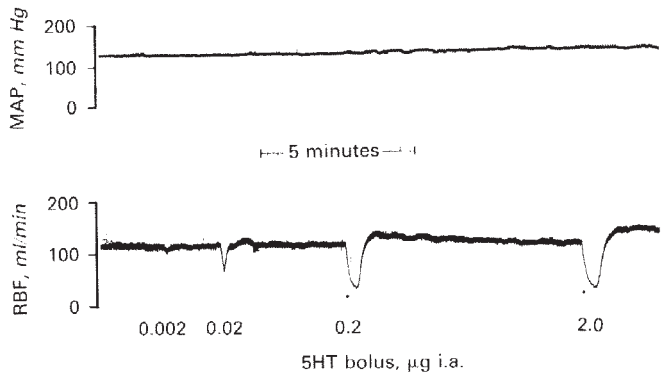

Fig. 1. *Tracing of blood pressure (MAP) and renal blood flow (RBF) response to serial doses of (5HT) injected into the renal artery.* Note the initial transient renal vasoconstriction followed by vasodilatation.

For the studies made with bolus injections, 0.02, 0.2 and 2.0 μg were delivered into the renal artery as a bolus by adding each to the constant infusion in volumes of 0.1 ml. Thereafter, constant infusions of 5HT at 3 and 30 μg per minute were made. The latter dose produced the largest change in renal blood flow without alterating systemic arterial blood pressure. Because the renal vascular response to 5HT was biphasic, both for injections (Fig. 1). and infusions (Fig. 2) dose response relationships were defined by employing the nadir blood flow value during the first vasoconstrictor phase, lasting 0 to 30 seconds, and the maximum value during the second or dilator phase (about two to three minutes) in the eight dogs.

During pilot studies, it was apparent that neither the response to 5HT delivered as a bolus or by infusion was modified by either ketanserin or methysergide, the 5HT antagonists (data not shown). Accordingly, the response to injections and infusions of 5HT were examined in the same eight dogs 40 minutes after the intrarenal administration of indomethacin (1.0 mg/kg).

The renal blood flow response to intrarenal injections of sodium arachidonate (200 to 1,000 μg) was used to verify blockade of prostaglandin synthetase in these experiments. The baseline response to sodium arachidonate was an increase in renal blood flow of 63 ± 8 ml/min; it was reduced to 12 ± 4 ml/min after indomethacin ($P < 0.001$).

Comparison with angiotensin II. Intrarenal infusions of a single dose of serotonin (Fig. 3A) and angiotensin II (Fig. 3B) were compared before and after indomethacin in six additional dogs. Four dogs received serotonin first, two received angiotensin II first. 5HT or AII were infused for a period of 10 minutes. Renal blood flow values used for analysis were obtained in the last minute prior to infusion of the test agent, 30 seconds, three minutes and six minutes after the onset of action. The 5HT dose used was 30 μg/min. AII was infused at a rate aimed at producing a comparable initial fall in renal blood flow to that produced by 5HT. Arterial doses of AII were 10 ng/min in two dogs and 30 ng/min in four dogs. Following completion of baseline infusion studies, indomethacin was administered as described for Protocol A. The 10 minute infusions of 5HT and AII were repeated in order to compare the magnitude of the prostaglandin dependent component of renal blood flow during administration of each agent.

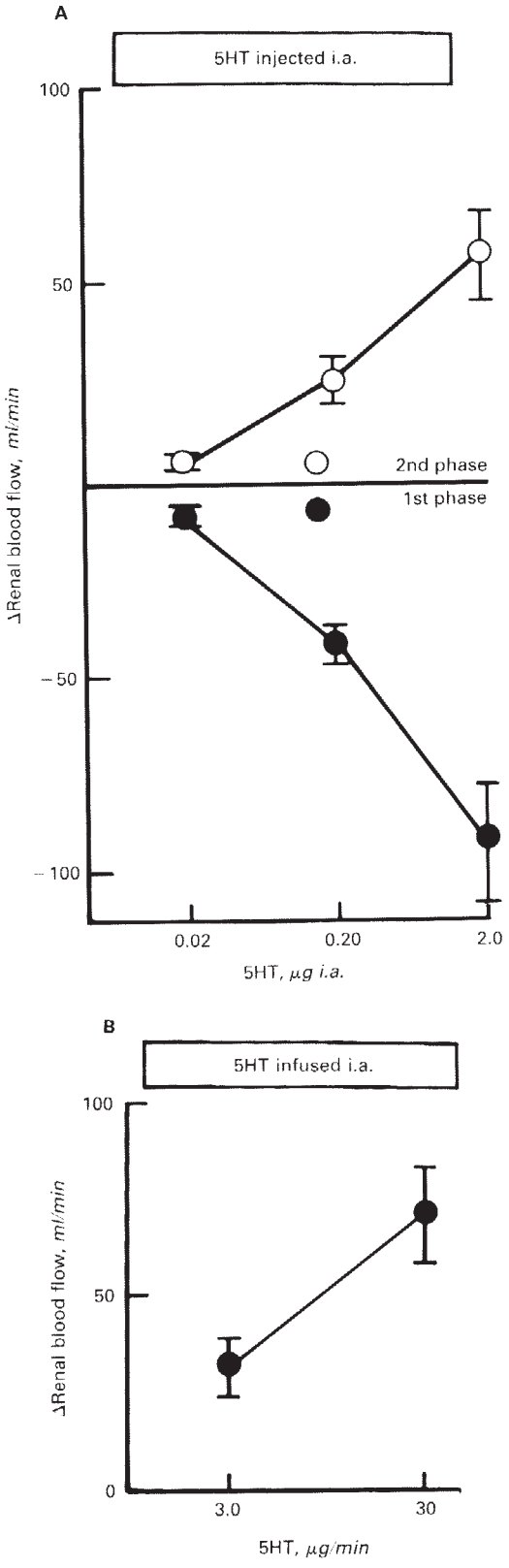

Fig. 2A *Dose–response relationships for renal blood flow when 5HT was injected into the renal artery as a bolus.* Note the transient, dose–related vasoconstriction, followed by dose–related vasodilatation. **B.** Relationship between 5HT dose infused and the sustained increase in renal blood flow. Larger doses than those shown induced hypotension.

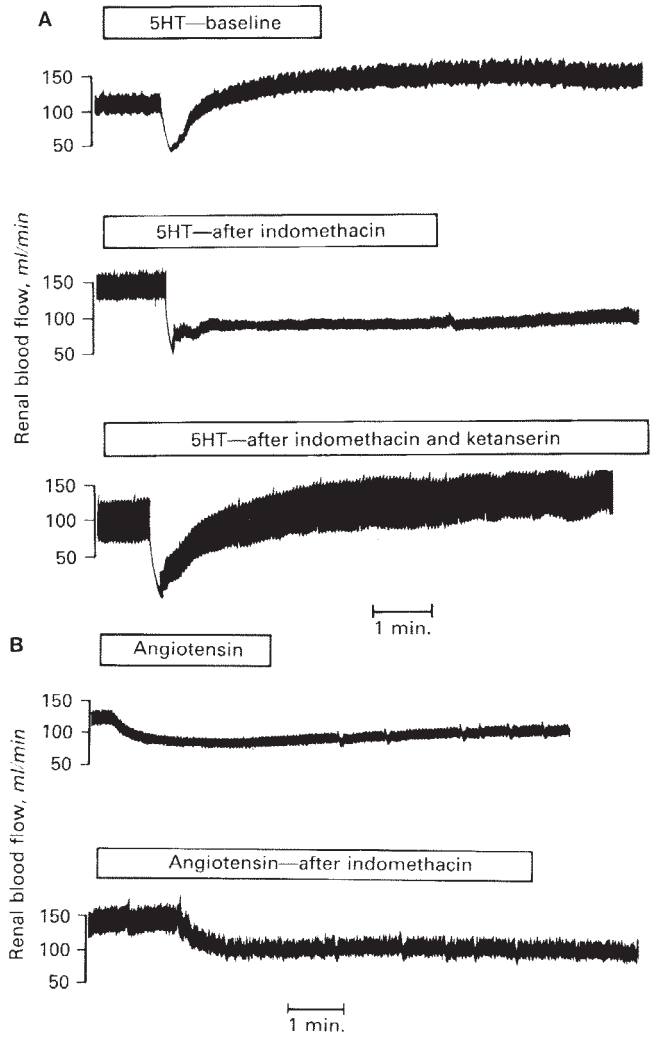

Fig. 3A. *Tracing of the renal blood flow response to serotonin infused into the renal artery.* Note the initial, transient vasoconstriction followed by sustained vasodilatation (top panel). In the same dog, after treatment with indomethacin, note the sustained vasoconstriction replacing the secondary, vasodilator phase (middle panel). Administration of ketanserin did not modify the initial vasoconstrictor response to serotonin, but blocked completely the sustained serotonin–induced vasoconstriction (lower panel). **B.** The renal vascular response to angiotensin infused into the renal artery prior to and (upper panel) and following (lower panel) treatment with indomethacin.

Effect of 5HT antagonists after indomethacin. Although ketanserin failed to modify renal vascular responses to 5HT in the absence of indomethacin as noted above, the striking influence of indomethacin on the renal vascular response to 5HT led us to re-examine the effect of 5HT antagonists on the renal vascular response when complicating indomethacin–responsive reactions had been blocked.

Ketanserin was administered intravenously in graded doses from 10 to 1,000 μg/kg, and methysergide in graded doses from 100 to 1,000 μg/kg. Ketanserin was administered first to five dogs, and methysergide was administered first to two dogs. Three of the dogs which had received ketanserin then received methysergide.

Table 1. Comparison of renal blood flow responses to serotonin before and after indomethacin (IND) in eight anesthetized dogs

	Baseline Q	Q (10 sec)	Q (3 min)
Pre IND	131 ± 19	46 ± 13**	196 ± 29*
Post IND	115 ± 15	30 ± 8**	86 ± 15**
P#	NS	NS	0.001

Abbreviations are: Q, renal blood flow, ml/min; IND, indomethacin; #P for difference between pre- and post-indomethacin.
Symbols are: * $P < 0.015$ vs. baseline; ** $P < 0.005$ vs. baseline.

Infusions of 5HT were repeated 15 minutes after the administration of each antagonist.

Responses of renal blood flow to phenylephrine (1 to 30 μg) injected into the renal artery were also made prior to and following ketanserin and methysergide administration, in search of evidence of alpha adrenergic blockade with the doses employed.

Analysis. Infusion of both serotonin and angiotensin II produced transient changes in renal blood flow which were followed by adjustments over the ensuing three to five minutes (see tracings, Figs. 1 and 3). Analysis was therefore performed by comparing baseline, 30 second, three minute and six minute values of renal blood flow by ANOVA. Mean values are presented with the standard error of the mean as the index of dispersion. The null hypothesis was rejected when P was less than 0.05.

Drugs. Indomethacin was provided by Merck, Sharp and Dohme (West Point, Pennsylvania, USA). Serotonin creatinine sulfate was obtained from Sigma Chemical Company (St. Louis, Missouri, USA). Sodium arachidonate was prepared by stirring arachidonic acid (Nu Check Prep Inc, Elysian, Minnesota, USA) in 100 mM sodium carbonate under N_2 gas. Ketanserin was provided by Janssen Pharmaceuticals, Piscataway, New Jersey. Methysergide was provided by Sandoz Pharmaceuticals, East Hanover, New Jersey. Drug doses were calculated as the base rather than the salt.

Results

Protocol A. Renal actions of 5HT before and after indomethacin

Mean arterial pressure was 137 ± 8 mm Hg before interventions and did not change significantly during serotonin administration in the doses used for analysis or after indomethacin treatment.

The renal vascular response to bolus injections of 5HT was complex, an initial vasoconstrictor response being followed by a flow overshoot and a vasodilator response (Figs. 1 and 2). Both the initial vasoconstrictor response and the delayed vasodilator response were dose–related after bolus injections with a threshold response at a dose below 2.0 ng. Responses to doses larger than 2 μg were not assessed because of complicating systemic arterial hypotension.

During 5HT infusion the initial, vasoconstrictor response strikingly resembled that seen during bolus injection (Fig. 3). The secondary vasodilator response, however, differed in that a larger and more sustained renal blood flow increase occurred; the relation between the 5HT dose infused and the sustained

Table 2. Effect of indomethacin on intrarenal bolus injections of 5HT[a]

		0.02 μg	0.20 μg	2.0 μg
	Phase 1 (0—30 sec)	−10 ± 2	−42 ± 5	−93 ± 16
	Phase 2 (30—60 sec)	4 ± 1	26 ± 5	58 ± 11
Indomethacin	Phase 1 (0—30 sec)	−8 ± 4	−36 ± 6	−85 ± 15
	Phase 2 (30—60 sec)	3 ± 1	8 ± 2*	16 ± 8*

* $P < 0.05$ vs. Phase 2 before indomethacin.
[a] Values are Δ renal blood flow from baseline in ml/min, $N = 8$.

Table 3. Comparison of indomethacin effect on intrarenally infused 5HT and angiotensin II in six dogs

	Baseline	30 sec	6 min
5HT	141 ± 23	68 ± 7	215 ± 35
5HT & Ind	149 ± 15	69 ± 8	103 ± 24
AII	139 ± 17	78 ± 10	112 ± 13
AII ± Ind	147 ± 17	71 ± 19	78 ± 16

Values are renal blood flow (ml/min).
Symbol is: * $P < 0.005$ vs. Δ Q 6 min for 5 HT

increase in renal blood flow is shown in Figure 2B. Again, the attempt to use larger doses produced hypotension.

Indomethacin administration converted the second vasodilator phase following 5HT infusions to sustain vasoconstriction in every case (Fig. 3A, Table 1). After three minutes of constant infusion of 5HT at 30 micrograms per minute, for example, indomethacin administration was responsible for a net difference of −110 ± 7 ml/min ($P < 0.005$). Indomethacin administration did not influence the magnitude of the first, vasoconstrictor phase.

Essentially similar effects were seen on the responses to bolus injections of 5HT after indomethacin administration. No alteration of the first phase of vasoconstriction was seen, but significant blunting of the second, vasodilator phase was evident (Table 2).

Protocol B: Comparison with angiotensin

This protocol was designed to compare the influence of indomethacin administration on the sustained renal vascular response to angiotensin II and to serotonin in doses that produced an initial renal blood flow fall in the neighborhood of 50%. Although indomethacin administration exerted a similar directional influence on the sustained renal vascular response to angiotensin (Fig. 3B) and to serotonin (Fig. 3A), there were quantitative differences in the response (Table 3). In both cases, the vasoconstrictor response faded, but substantially more rapidly and more completely during serotonin infusion than during angiotensin II infusion. Six minutes after initiating serotonin infusion, the absolute difference in blood flow to the kidney was 112 ± 26 ml/min when serotonin was employed, and 34 ± 14 ml/min when angiotensin II was employed ($P < 0.005$; Table 3).

Table 4. Mean renal blood flow before and at intervals during 5HT infusion and the influence of ketanserin and methysergide

	N	Baseline	30 Sec	6 Min
I	5	141 ± 18	69 ± 5	106 ± 26
I & K	5	130 ± 15	39 ± 10	181 ± 30
I & M	5	169 ± 32	102 ± 40	165 ± 32

Abbreviations are: I, indomethacin; K, ketanserin; M, methysergide.
Symbols are: * $P < 0.005$; ** $P < 0.05$.

Protocol C: The influence of serotonin antagonists

Neither ketanserin nor methysergide influenced the initial serotonin–induced decrease in renal blood flow, but in indomethacin–treated dogs, ketanserin induced striking reversal of the sustained vasoconstriction (Fig. 3A and Table 4). Ketanserin's effect was complete in that a sustained increase of renal blood flow above baseline was restored despite indomethacin pretreatment, with a threshold ketanserin dose of less than 1.0 μg/kg (Fig. 4).

The influence of ketanserin on the renal vascular response to phenylephrine injected into the renal artery, as an index of ketanserin's alpha adrenergic blocking action, is shown in Figure 5. Phenylephrine when employed without inhibitors induced a dose–related reduction in renal blood flow. Ketanserin at a dose of 10 μg/kg had no influence on response, but a dose of 100 μg/kg clearly blunted the renal vascular response to phenylephrine ($P < 0.01$). Thus, the dose for alpha blockade (Fig. 5) was substantially higher than the ketanserin dose required to block the sustained renal vasoconstriction that occurs during serotonin infusion following indomethacin (Fig. 4).

Further addition of methysergide, the nonselective 5HT antagonist reduced the late increase in renal blood flow which had been restored by ketanserin (Table 4). When methysergide was employed alone after indomethacin, an intermediate response was observed; a sustained increase of renal blood flow above baseline did not occur. In the five animals which received methysergide after indomethacin, there was no difference in renal blood flow after six minutes of 5HT infusion from baseline. The vasodilator response of 5HT had been abolished.

Neither ketanserin nor methysergide changed renal blood flow when administered alone, in the basal state.

Discussion

These studies may clarify apparently divergent reports on the complex renal vascular responses to serotonin [1–9, 17]. We have identified two actions that result in net vasoconstriction and two actions that result in net vasodilatation. The two constrictor elements include immediate, transient, dose–related vasoconstriction which was not modified by any maneuver employed in the study, and a sustained element. The sustained vasoconstriction was apparent only after prostaglandin synthetase inhibition and was reversed by ketanserin, the 5HT-2 antagonist. In the intact dog, dose–dependent net vasodilatation was the dominant response to serotonin, a response that disappeared after prostaglandin synthetase inhibition. There was clearly an additional vasodilator response unrelated to prostaglandins that was apparent only after the administration

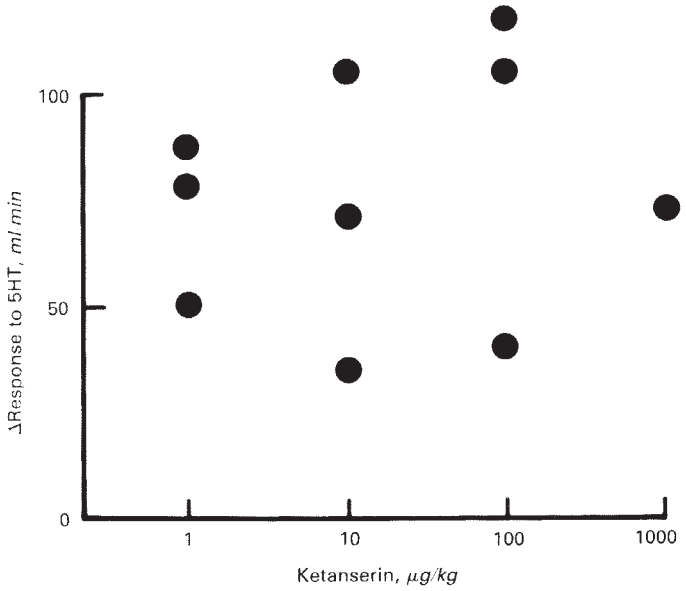

Fig. 4. *Relation between ketanserin dose and the difference in the sustained renal response to 5HT infusion prior to and after indomethacin.* The increase in renal blood flow reflects blockade of serotonin-induced vasoconstriction, and the threshold ketanserin dose is less than 1 μg/kg.

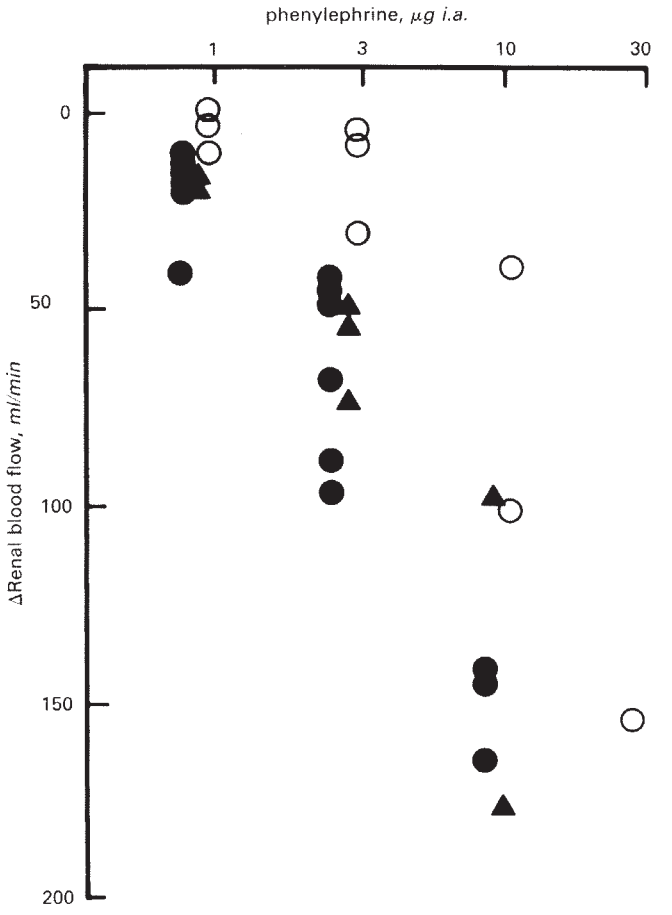

Fig. 5. *Relation between phenylephrine dose injected into the renal artery and change in renal blood flow.* Note that ketanserin at 10 μg/kg did not influence the response, but ketanserin at 100 μg/kg blunted the response, reflecting alpha adrenergic blockade induced by ketanserin at doses higher than those required for blockade of serotonin receptors. Symbols are: (●) no inhibitors; (▲) ketanserin 10 μg/kg; (○) ketanserin 100 μg/kg.

of ketanserin; this vasodilator response was attenuated by methysergide. Taken in all the data are compatible four separable components in the renal vascular response, and the pharmacological observations may account for three. Only the initial, transient, dose-dependent vasoconstriction lacks a pharmacological explanation. It is not surprising, therefore, that the literature on the renal vascular response to serotonin has been divergent.

One would anticipate from these observations, for example, that studies in which a bolus of serotonin was employed would reveal primarily vasoconstriction. This is compatible with many reports [4–6]. Further, it might be expected that more sustained infusions of serotonin would produce more variable results, again as has been reported [7–11].

The ability of prostaglandin synthetase inhibitors to sensitize the renal blood supply to angiotensin and to result in a more sustained renal vascular response to angiotensin has been widely documented [10, 11], and represents the paradigm of modulation by prostaglandins of the response to vasoconstrictors. In this study that observation has been confirmed and extended. The action of indomethacin on the response to serotonin was similar in direction, but strikingly larger in magnitude, whatever sequence was employed to administer the two vasoconstrictor agents. Within seconds net vasodilatation occurred with serotonin, whereas angiotensin's vasoconstrictor response was better sustained in the same dogs. The most straightforward explanation is that serotonin is more effective than angiotensin in causing release of a vasodilator prostaglandin, although in the absence of a direct measurement of these hormones the conclusion remains speculative. Although indomethacin is known to have a wide range of pharmacologic actions [18], the parallelism between its influence on the response to angiotensin II and the response to serotonin certainly supports the obvious possibility that indomethacin acted by virtue of that action in the study. Serotonin has been shown, moreover, to induce prostaglandin release elsewhere [19].

The vasodilator effect of serotonin was substantial after administration of ketanserin to the indomethacin-treated animals, suggesting a large, direct serotonin-mediated dilator action, an action that is independent of either the 5HT-2 receptor or prostaglandins. This vasodilatation was reversed by methysergide. Methysergide is a complex antagonist, having substantial partial agonist, serotonin-like activity [20]. Under the conditions of our experiment, however, the partial agonist activity would have been anticipated to be vasodilator. It seems more likely that methysergide was acting on an unrelated serotonin receptor responsible for vasodilatation. We have made similar observations on blood flow responses in the circulation of the limb [15]. The term 5HT-1 receptor was coined to apply to the central nervous system [21], and has not hitherto been applied to responses in the circulation. Identical actions of methysergide on dilator responses to serotonin in two circulatory beds, and the finding of a similar effect in isolated

vessels under specialized conditions [22] raises the interesting possibility that there is, indeed, a 5HT-1 receptor in the circulation which leads to vasodilatation. The contribution of that mechanism to the magnitude of the dilator response differs from vascular bed to vascular bed. In the limb, for example, prostaglandin synthetase inhibition does not modify the dilator response to serotonin; in that vascular bed a mechanism responsive to methysergide accounted for all of the vasodilatation [15].

Ketanserin is known to be an alpha–adrenergic blocking agent, in addition to its ability to block 5HT-2 receptor, although in general higher doses or concentrations are required [16, 20]. In this study, the ketanserin dose required to blunt serotonin–induced renal vasoconstriction after indomethacin was less than 1.0 μg/kg, and there was little evidence of further blockade with higher doses. The ketanserin dose required to induce alpha–adrenergic blockade, with phenylephrine as the index, was ten to 100–fold higher. It seems unlikely, therefore, that the sustained renal vasoconstrictor response to serotonin after indomethacin reflects an action of serotonin on alpha–adrenergic receptors. It is also clear, if ketanserin is to be employed as a pharmacologic probe to ascertain the role of 5HT in syndromes characterized by renal vasoconstriction, that consideration of dose will be important.

Serotonin–induced vasoconstriction was sufficient in degree and was sufficiently well sustained to raise the possibility that it could play a role in syndromes such as the hemolytic uremic syndrome and some of the forms of inflammatory renal disease in which platelet disruption and serotonin release occurs [23, 24]. Among the strategies designed to reverse the potential contribution of platelets to these syndromes, none have included ketanserin, the 5HT-2 antagonist. Ketanserin antagonizes the vasoconstrictor properties of serotonin without antagonizing the vasodilator properties, a characteristic not shared by the widely–studied serotonin antagonist, methysergide [15, 25]. Ketanserin, moreover, has a pronounced inhibitory influence on platelet aggregation, also apparently via the 5HT-2 receptor blockade [26].

Our data suggest that prostaglandins may ameliorate the otherwise deleterious effects of serotonin on the renal circulation. Spontaneous variation in the capacity of the kidney to synthesize vasodilator prostaglandins, disease–related reduction in synthetic capacity or release, or pretreatment with non-steroidal anti-inflammatory agents, may predispose to the potentially destructive vasoconstrictor effects of serotonin. Anti-inflammatory drugs are well documented to provoke renal functional deterioration in patients with conditions associated with ongoing intravascular platelet aggregation. Our observations may explain, for example, the manner in which patients with active lupus nephritis or glomerulonephrisit of other etiologies are particularly susceptible to decreases in renal function from indomethacin–like drugs [28, 29].

Acknowledgments

We acknowledge the technical assistance of Patricia Dunning and Gary Melanson and the manuscript preparation by Diana Page. This study was supported by grants from the National Institutes of Health (CA 32849, HL 07236, HL 14944, HL 05832) and from the National Aeronautics and Space Administration (NAG 9–17, Suppl. 6).

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References

1. Adler S: Serotonin and the kidney, in *Serotonin in Health and Disease*, edited by Essman WB, New York, Spectrum Publications, Inc., 1977, pp. 99–137.
2. Spinazzola AJ, Sherrod TR: The effects of serotonin (5-hydroxytryptamine) on renal hemodynamics. *J Pharmacol Exp Ther* 119:114, 1957
3. McCubbin JW, Kaneko Y, Page IH: Inhibition of neurogenic vasoconstriction by serotonin. Vasodilator action of serotonin. *Circ Res* 11:74–83, 1962
4. Erspamer V: Pharmacological studies on enteramine (5-hydroxytryptamine). Influences of sympathomimetic and sympatholytic drugs on the physiological and pharmacological actions of enteramine. *Arch Int Pharmacodyn Ther* 93:293–316, 1953
5. Vyden JK, Lent D, Nagasawa K, Carvahlo M, Serruya A, Corday E: The effects of serotonin on regional hemodynamics in the vascular system. *J Clin Pharm* pp. 434–441, 1974
6. Emannel 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
7. Caldicott WHH, Hollenberg NK, Abrams HL: Characteristics of response of renal vascular bed to contrast media. Evidence for vasoconstriction induced by renin–angiotensin system. *Invest Radiol* 5:539–547, 1970
8. Bunag RD, Page IH, McCubbin JW: Neural stimulation of release of renin. *Circ Res* 19:851–858, 1966
9. Page, IH, McCubbin JW: The variable arterial pressure response to serotonin in laboratory animals and man. *Circ Res* 1:354–362, 1953
10. Levenson DJ, Simmons CE, Jr, Brenner, BM: Arachidonic acid metabolism, prostaglandins and the kidney. *Am J Med* 72:354–374, 1982
11. Dunn MJ, Zambraski EJ: Renal effects of drugs that inhibit prostaglandin synthesis. *Kidney Int* 18:609–622, 1980
12. Brazenor RM, Angus JA: Actions of serotonin antagonists on dog coronary artery. *Eur J Pharmacol* 81:569–576 (abstract), 1982
13. Van Nueten JM: Serotonergic amplification mechanisms in vascular tissues, *5-Hydroxytryptamine in peripheral reactions*, DeClerck F, Vanhoutte PM, New York, Raven Press, 1982, pp. 77–82.
14. Vanhoutte PM: 5-Hydroxytryptamine, vasospasm and hypertension, *5-Hydroxytryptamine in peripheral reactions*, DeClerck F, Vanhoutte PM (eds). New York, Raven Press, 1982, pp. 163–174
15. Blackshear JL, Orlandi C, Garnic JD, Hollenberg NK: Differential large and small vessel responses to serotonin in the dog hind–limb *in vivo*: Role of the 5HT-2 receptor. *J Cardiovasc Pharmacol* 7:42–49, 1985
16. Van Nueten JM, Janssen PAJ, de Riddler W, Vanhoutte PM: Interaction between 5-hydroxytryptamine and other vasoconstrictor substances in the isolated femoral artery of the rabbit; effect of ketanserin (RY1 468). *Eur J Pharmacol* 77:281–287, 1982
17. Haddy FJ, Gordon P, Emanuel DA: Influence of tone upon responses of small and large vessels to serotonin. *Circ Res* 7:123–130, 1959
18. Dunn MJ, Hood YI: Prostaglandins and the kidney. *Am J Physiol* 233:169–184, 1977
19. Alabaster VA, Bakhle YS: The release of biologically active substances from isolated lungs by 5-hydroxytryptamine and tryptamine. *Proc Br Pharmacol Soc* pp. 582P–583P, 1970
20. Van Nueten JM, Janssen PAJ, Van Beek J, Xhonneaux R, Verbeuren TJ, Vanhoutte PM: Vascular effects of ketanserin (R41 468), a novel antagonist of $5HT_2$ serotonergic receptors. *J Pharmacol Exp Ther* 218:217–230, 1981
21. Peroutka SJ, Snyder SH: Multiple serotonin receptors and their physiological significance. *Fed Proc* 42:213–217, 1983
22. McGrath MA: 5-Hydroxytryptamine and neurotransmitter release in canine blood vessels. Inhibition by low and augmentation of high concentrations. *Circ Res* 41:428–435, 1977
23. Andrassy K, Ritz E, Mayerhoff T, Bommer J: What is the evidence for activated coagulation in glomerulonephritis? *Am J Nephrol* 2:293–300, 1982

24. KORDENAT RK, KEZDI P: Serotonin blockade during experimental coronary thrombosis. *Am Heart J* 97:329–338, 1979
25. COHEN RA, SHEPHERD JT, VANHOUTTE PM: 5-Hydroxytryptamine can mediate endothelium–dependent relaxation of coronary arteries. *Am J Physiol* 245:H1077–H1080, 1983
26. DE CLERCK F, DAVID JL, JANSSEN PAJ: Serotonergic amplification mechanisms in blood platelets, *5-Hydroxytryptamine in peripheral reactions*, edited by DECLERCK F, VANHOUTTE PM, New York, Raven Press, 1982, pp. 83–94
27. HOLLENBERG NK, HARRINGTON DP, GARNIC JD, ADAMS DF, ABRAMS HL: Renal angiography in the oliguric state, in *Abrams Angiography*, Boston, Little, Brown and Company, 1983, pp. 1299–1325
28. KIMBERLY RP, GRILL JR, BOWDEN RE, KEISER HR, PLOTZ PH: Elevated urinary prostaglandins and the effects of aspirin on renal function in lupus erythematosus. *Ann Int Med* 89:336–341, 1978
29. CIABATTONI G, CINOTTI GA, PIERUCCI A, SIMONETTI BM, MANZI M, PUGLIESE F, BARSOTTI P, PECCI G, TAGGI F, PATRONO C: Effects of sulindac and ibuprofen in patients with chronic glomerular disease. *N Engl J Med* 310:279–283, 1984