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Renal vasoconstrictor response to 5-hydroxytryptamine in the in situ autoperfused rat kidney: involvement of angiotensin II and the 5-HT_2 receptor activation

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Abstract

Using a number of agonist and antagonist compounds, we attempted to characterize the responses and receptors involved in the effects of 5-hydroxytryptamine (5-HT) in the in situ autoperfused rat kidney. An intra-arterial (i.a.) bolus injection of 5-HT (0.0125 to 0.1 μg/kg) increased renal perfusion pressure in a dose-dependent way but did not change the systemic blood pressure. The 5-HT_2 receptor agonist, (1-(3-chlorophenyl) piperazine), *m*-CPP, caused a local vasoconstrictor effect in the autoperfused rat kidney. An intra-arterial injection of 5-carboxamidotryptamine, 5-CT and 1-(*m*-chlorophenyl)-biguanide (*m*-CPBG) did not modify the renal perfusion pressure. The vasoconstrictor effect elicited by 5-HT and *m*-CPP was significantly decreased by ritanserin, enalapril and losartan but was not modified by prazosin, propranolol or indomethacin pretreatment. Our data suggest that the vasoconstrictor serotonergic response induced in the in situ autoperfused rat kidney is mediated through angiotensin II activation by a local 5-HT_2 receptor mechanism. © 1997 Elsevier Science B.V.

Keywords: 5-HT (5-hydroxytryptamine, serotonin); 5-HT receptor agonists; Renal blood flow; Kidney, autoperfused, rat; Angiotensin II

1. Introduction

Since the discovery of 5-hydroxytryptamine, there has been substantial interest in its renal circulation, but the effects of this biogenic amine on the kidney remain controversial. Vasodilation and vasoconstriction of renal vessels after pharmacological doses of 5-HT have been reported by several authors. A 5-HT_2 vasoconstrictor effect has been shown in vivo (Endlich et al., 1993) and in vitro, in rat kidney preparations (Charlton et al., 1984; Janssen and Van Nueten, 1986; Verbeuren et al., 1991), also in conscious rabbits (Wright and Angus, 1987) and in an in vivo canine renal vasculature preparation (Blackshear et al., 1991). Renal vasodilation, through 5-HT_1-like activation, has also been observed in vivo (Endlich et al., 1993) and in vitro rat preparations (Charlton et al., 1984). There are conflicting claims about the 5-HT receptors mediating the effects of 5-HT on the renal vasculature. For the canine renal vasculature, Blackshear et al. (1986) reported 5-HT_1-like receptor-mediated vasodilation and 5-HT_2 receptor-mediated vasoconstrictor components while Shoji et al. (1989) concluded that 5-HT_2 receptors mediate vasodilation and that 5-HT_1-like receptors are involved in vasoconstriction.

Recently, the interaction of prostaglandins and 5-HT has been investigated in the canine kidney (Blackshear et al., 1986, 1991; Ding et al., 1989). Interaction between 5-HT and prostaglandin has also been reported for the isolated perfused rat kidney (Tuncer and Vanhoutte, 1991). However, in the intact rat kidney, 5-HT was found to act independently of the prostaglandin system (Ding et al., 1989).

It is known that both direct and indirect 5-HT receptor agonists increase arterial pressure and plasma renin activity through central and/or peripheral mechanisms (Van De Kar et al., 1981; Alper and Snider, 1987; Zink et al., 1990; Takahashi et al., 1991). However, 5-HT receptor subtypes in renal vascular beds have not been defined due to the conflicting results obtained with different species as well as different experimental models.

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The present study was designed to define the 5-HT receptor subtypes of renal vascular beds in the rat kidney in vivo and to demonstrate the possible existence of a peripheral mechanism that can be activated by exogenous 5-HT or 5-HT receptor agonists in the kidney. 5-HT and 5-HT receptor agonists were injected directly into the artery of the left kidney in anaesthetized rats. A possible interaction between serotonergic mechanisms and sympathetic renal nerve stimulation in the anaesthetized rat is discussed.

2. Material and methods

2.1. Animal preparation

Male Wistar rats, weighing 350–400 g, from the animal house of the Faculty of Pharmacy of the University of Salamanca were used in all experiments. The rats were anaesthetized with sodium pentobarbital (60 mg/kg, i.p.). After the induction of anaesthesia, a tracheotomy was performed and catheters were placed in the right and left carotid arteries. The right carotid artery was cannulated for blood pressure measurement using a Spectramed model P23 × L pressure transducer and a Grass model 7 Physiograph recorder. The penis vein was cannulated for drug administration. The animals were kept warm with a heating lamp.

Rats were prepared for in situ perfusion of the left kidney. The vascular beds were perfused using an extracorporeal circuit and a constant flow Gilson peristaltic pump. The left carotid artery was cannulated with the inflow end of the extracorporeal flow line. The abdominal aorta was exposed by midline laparotomy and deflection of the intestines to the right side of the animal. A loose tie was placed around the aorta above the left renal artery but below the origin of the right renal and superior mesenteric arteries. Additional ties were placed around the aorta 1 cm below the left renal artery and 1 cm above the iliac bifurcation. Heparin sodium (5 mg/kg) was then given intravenously and an intravenous infusion of normal saline (0.9% NaCl) was initiated at a rate of 2 ml/h and continued throughout the experiment.

When the aortic tie above the left renal artery was tightened, blood immediately began to flow from the carotid to the left renal artery; the circuit was thus established without interruption of blood flow to the kidney. Blood was pumped from the right carotid artery to an aortic pouch from which the left renal artery was the only outlet (Fink and Brody, 1978; Dupont et al., 1986; Roquebert et al., 1992).

The distal portion of the external circuit was connected to a Spectramed model P23 × L pressure transducer for measurement of perfusion pressure which was recorded on a Grass model 7 Physiograph recorder. At the beginning of each experiment, the flow was adjusted to make the perfusion pressure equal to the systemic pressure. The flow was kept constant throughout the experiment, changes in the perfusion pressure reflecting the changes in vascular resistance. The flow rate through the renal vascular beds ranged from 2 to 2.9 ml/min (Roquebert et al., 1992). In all experiments atropine (1 mg/kg) was administered intravenously before the saline infusion was started in order to block the cholinergic effect.

2.2. Experimental protocols

After a 15 min period allowed for blood pressure and perfusion pressure to stabilize, the next experiments were performed using five animals to evaluate each dose of agonist or antagonist and each animal preparation to evaluate only one agonist or antagonist:

(1) 5-HT, 5-carboxamidotryptamine, 5-CT, 1-(3-chlorophenyl) piperazine, *m*-CPP, or 1-(*m*-chlorophenyl)-biguanide, *m*-CPBG, at doses of 0.0125, 0.025, 0.05 and 0.1 mg/kg were administered locally via the distal cannula, intra-arterially (i.a.), by bolus injection of a maximum volume of 10 μl using a microsyringe (Exmire microsyringe), 5 min elapsing between each drug dose.

(2) In order to analyze the mechanism of action of 5-HT, various antagonists were administered intravenously. These antagonists (ritanserin 1 mg/kg, propranolol 2 mg/kg, prazosin 0.1 mg/kg, enalapril 5 mg/kg, losartan 1 mg/kg and indomethacin 2 mg/kg) were administered 10–15 min before i.a. administration of 5-HT or *m*-CPP.

(3) To confirm the ability of enalapril to inhibit the activity of 5-HT and to assess the specificity of action of enalapril on the reactivity of angiotensin I and II, various doses of this antagonist (1–10 mg/kg) were administered before the i.a. administration of either 5-HT or angiotensin II (0.0125, 0.025, 0.050 and 0.1 μg/kg) or angiotensin I (0.1 μg/kg). The antagonists, losartan and ritanserin (1 mg/kg), were also administered before i.a. administration of angiotensin II (0.0125, 0.025, 0.050 and 0.1 μg/kg) and angiotensin I (0.1 μg/kg).

(4) In a further series of experiments, the influence of locally administered 5-HT (0.1–50 μg/kg) and *m*-CPP (10 μg/kg) on the increases in perfusion pressure induced by electrical stimulation was studied. To stimulate the periarterial renal nerves, a bipolar electrode was placed adjacent to the aorta. Electrical stimulation was performed using square wave pulses from a Cybertec Stimulator CS-9 (10 V; 1 ms; 2, 4, 6 Hz). Stimulation was continued at each frequency until the response was maximal (10 s). Basal perfusion pressure was restored immediately after interruption of the stimulation.

Immediately after the first series of stimulations, saline (0.5 ml/kg) was injected and, after 5 min, a second frequency response curve was obtained. 5 min later, 5-HT (0.1–50 μg/kg) or *m*-CPP (10 μg/kg) was administered

locally and immediately afterwards a third frequency of stimulations was applied.

2.3. Drugs used

The following drugs were used: pentobarbital sodium (Sigma), heparin sodium (Roche), atropine sulphate (Scharlau), 5-hydroxytryptamine-creatinine sulphate (Sigma), 5-carboxamidotryptamine maleate, 5-CT (Research Biochemicals International), 1-(3-chlorophenyl)piperazine dihydrochloride, *m*-CPP (Research Biochemicals International), 1-(m-(chlorophenyl)biguanide hydrochloride, *m*-CPBG (Research Biochemicals International), angiotensin I (Sigma), angiotensin II (Sigma), ritanserin (Janssen Farmaceutica), D-L-propranolol hydrochloride (ICI Pharmaceuticals), enalapril maleate (Merck, Sharp and Dohme), indomethacin (Merck, Sharp and Dohme), prazosin (Pfizer), losartan (Merck). All drugs used were dissolved in distilled water at the time of the experiments, with the exception of angiotensin I and II, dissolved in saline solution and ritanserin and *m*-CPP, which were dissolved in 0.04 mol/l lactic acid and 0.01 M HCl, respectively.

2.4. Statistics

The results are given as means ± S.E.M. of five experiments. Changes in renal vascular resistance are given as increases, in mmHg, of perfusion pressure in comparison to control values. Statistical significance was calculated by means of the unpaired Student *t*-test. Values of $^{a}P < 0.05$, $^{b}P < 0.01$ and $^{c}P < 0.001$ were considered significant.

3. Results

3.1. Renal vascular effect of 5-hydroxytryptamine receptor agonists: 5-HT, m-CPP, 5-CT and m-CPBG

The mean resting blood pressure and perfusion pressure values in these studies were 90.5 ± 5.4 mmHg ($n = 120$) and 91.42 ± 3.2 mmHg ($n = 120$), respectively.

In the first group of experiments, local injection of graded doses of 5-HT (0.0125, 0.025, 0.05 and 0.1 μg/kg) had no effect on systemic blood pressure but increased perfusion pressure in in situ autoperfused rat vascular beds in a dose-dependent way (10.5 ± 2.00; 17.25 ± 3.36; 22.75 ± 4.05 and 30.9 ± 6.45 mmHg) (Fig. 1). Likewise, at doses from 0.0125 to 0.1 μg/kg the selective 5-HT_2 agonist, *m*-CPP, increased the perfusion pressure by 9.69 ± 1.1; 17.5 ± 3.38; 24.06 ± 4.49 and 33.19 ± 5.62 mmHg, respectively (Fig. 1) without modifying blood pressure.

In contrast, neither systemic blood pressure nor perfusion pressure was modified by local administration of similar doses of 5-CT and *m*-CPBG, a 5-HT_1 and a 5-HT_3 receptor agonist, respectively (Fig. 1).

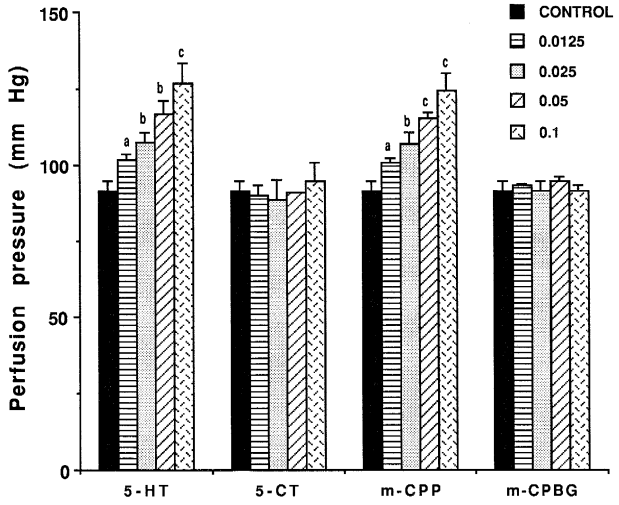

Fig. 1. Effect of renal intra-arterial administration of different doses of 5-HT receptor agonists (0.0125–0.1 μg/kg) on perfusion pressure in the in situ autoperfused rat kidney. 5-HT (5-hydroxytryptamine), 5-CT (5-carboxamidotryptamine), *m*-CPP ((1-(3-chlorophenyl) piperazine) and *m*-CPBG (1-(*m*-chlorophenyl)-biguanide). $^{a}P < 0.01$, $^{b}P < 0.05$ and $^{c}P < 0.001$ with respect to basal perfusion pressure.

3.2. Effect of antagonists on 5-HT or m-CPP renal vasoconstrictor-induced effect

Pretreatment with 1 mg/kg of the 5-HT_2 receptor antagonist, ritanserin, abolished the vasoconstrictor responses to 5-HT and *m*-CPP (Figs. 2 and 4).

In another series of experiments the effects of 5-HT and *m*-CPP after indomethacin (2 mg/kg) treatment were tested. During this pretreatment, no changes were observed in mean blood pressure. 10 min after intravenous adminis-

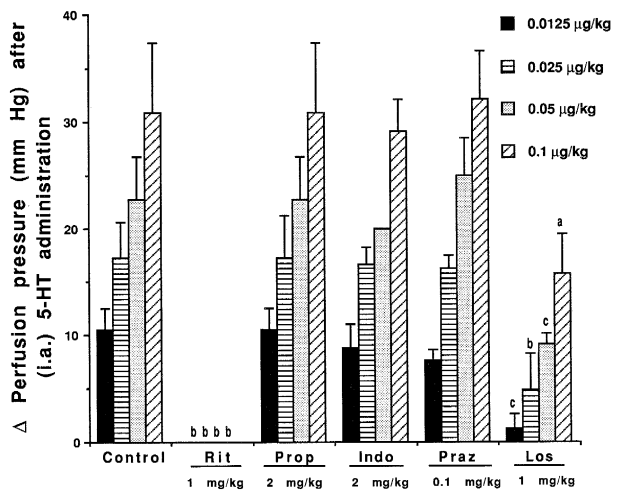

Fig. 2. Effect of ritanserin (Rit) 1 mg/kg, propranolol (Prop) 2 mg/kg, indomethacin (Indo) 2 mg/kg, prazosin (Praz) 0.1 mg/kg and losartan (Los) 1 mg/kg pretreatment on the renal vasoconstrictor effect induced by intra-arterial administration of 5-HT (0.0125–0.1 μg/kg) in the in situ autoperfused rat kidney. $^{a}P < 0.01$, $^{b}P < 0.05$ and $^{c}P < 0.001$ with respect to saline group, which received the same 5-HT doses without antagonist pretreatment.

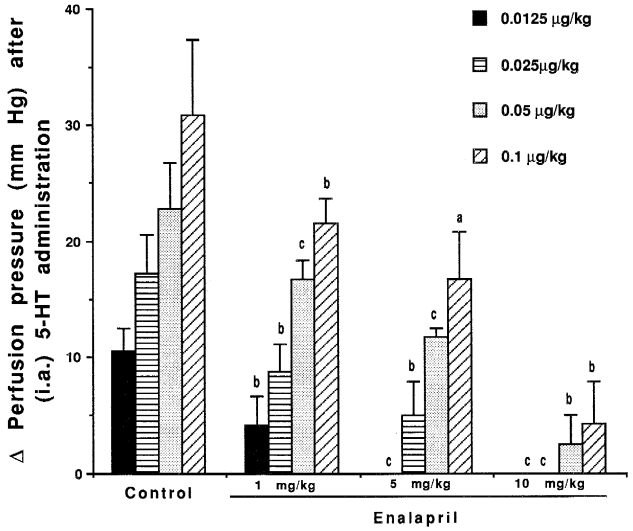

Fig. 3. Effect of enalapril (1, 5 and 10 mg/kg) pretreatment on the renal vasoconstrictor effect induced by intra-arterial administration of 5-HT (0.0125–0.1 μg/kg) in the in situ autoperfused rat kidney. $^{a}P < 0.01$, $^{b}P < 0.05$ and $^{c}P < 0.001$ with respect to saline group, which received the same 5-HT doses without antagonist pretreatment.

tration of indomethacin both 5-HT and *m*-CPP increased perfusion pressure (Figs. 2 and 4).

The possible role of α and β-adrenoceptors in the responses to 5-HT and *m*-CPP was determined by pretreatment with an α-adrenoceptor antagonist, prazosin (0.1 mg/kg, a dose that blocks adrenaline vasoconstriction in this experimental model), or D,L-propranolol (2 mg/kg), a non-selective β-adrenoceptor antagonist. The vasoconstrictor effects elicited by 5-HT and *m*-CPP were not affected by the α- or the β-adrenoceptor-blocking agent either (Figs. 2 and 4). However, as expected, prazosin alone slightly reduced both blood pressures (systemic and perfusion, data not shown) and propranolol elicited a slight and non-significant decrease in perfusion pressure.

In contrast, enalapril significantly attenuated 5-HT-induced vasoconstriction in the autoperfused rat kidney in a dose-dependent way (Fig. 3). A dose of 10 mg/kg of enalapril also inhibited the vasoconstrictor effect of *m*-CPP (Fig. 4). The vasoconstrictor effect of 5-HT was also inhibited by 1 mg/kg of losartan (Fig. 2).

3.3. Renal vascular effect induced by local angiotensin I or angiotensin II administration

Intra-arterial administration of angiotensin II increased perfusion pressure in the in situ autoperfused rat kidney in a dose-dependent way (Fig. 5) and this response, which was inhibited by 1 mg/kg of losartan, was not blocked by either enalapril (1 and 5 mg/kg) or ritanserin (1 mg/kg) pretreatment (Fig. 5). The antagonist, enalapril, blocked the response to i.a. administration of 0.1 μg/kg of angiotensin I (Fig. 6). Pilot experiments showed that graded dose–response curves could not be obtained with this agonist because of the rapid development of tachyphylaxis.

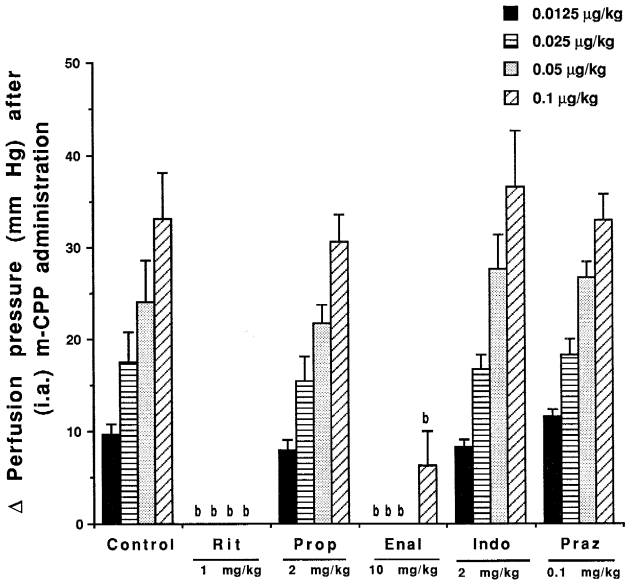

Fig. 4. Effect of ritanserin (Rit) 1 mg/kg, propranolol (Prop) 2 mg/kg, enalapril (Enal) 10 mg/kg, indomethacin (Indo) 2 mg/kg and prazosin (Praz) 0.1 mg/kg, pretreatment on the renal vasoconstrictor effect induced by intra-arterial administration of *m*-CPP (0.0125–0.1 μg/kg) in the in situ autoperfused rat kidney. $^{a}P < 0.01$, $^{b}P < 0.05$ and $^{c}P < 0.001$ with respect to saline group, which received the same *m*-CPP doses without antagonist pretreatment.

3.4. Influence of 5-HT or m-CPP on the vasoconstriction induced by renal electrical stimulation of the periarterial nerves

In another group of experiments, electrical stimulation of the sympathetic nerves induced reproducible, frequency-dependent increases in perfusion pressure (16.66

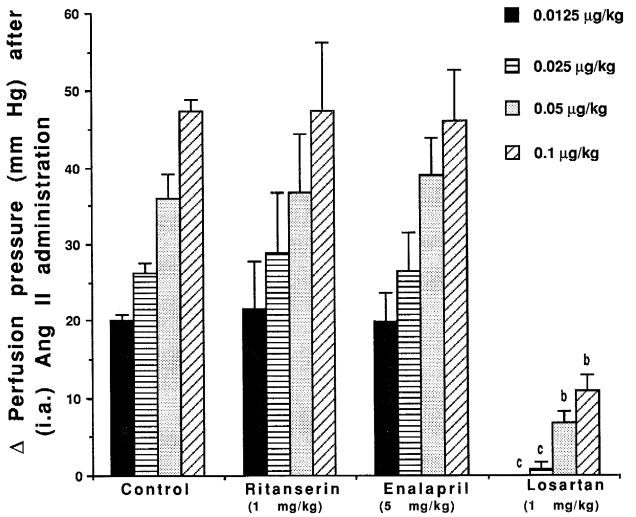

Fig. 5. Effect of renal intra-arterial administration of angiotensin II (0.0125–0.1 μg/kg) on perfusion pressure in the in situ autoperfused rat kidney and effect of enalapril (5 mg/kg), losartan (1 mg/kg) and ritanserin (1 mg/kg) pretreatment on this effect. $^{a}P < 0.01$, $^{b}P < 0.05$ and $^{c}P < 0.001$ with respect to saline group, which received angiotensin II doses without antagonist pretreatment.

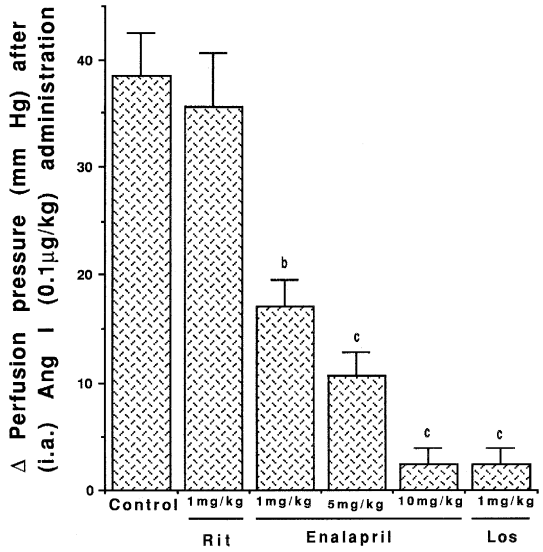

Fig. 6. Effect of renal intra-arterial administration of angiotensin I (0.1 μg/kg) on perfusion pressure in the in situ autoperfused rat kidney and effect of enalapril (1, 5 and 10 mg/kg), losartan (Los, 1 mg/kg) and ritanserin (Rit, 1 mg/kg) pretreatment on this effect. $^{a}P < 0.01$, $^{b}P < 0.05$ and $^{c}P < 0.001$ with respect to saline group, which received angiotensin I doses without antagonist pretreatment.

$\pm$ 1.78; 38.5 $\pm$ 3.45; 55.41 $\pm$ 6.13 mmHg for 2, 4 and 6 Hz, respectively). Graded doses (0.1–50 μg/kg) of 5-HT and 10 μg/kg of *m*-CPP had no effect on the increases in perfusion pressure brought about by electrical stimulation over the whole frequency range used with the autoperfused rat kidney (results are not shown).

4. Discussion

4.1. General

According to indications of Fink and Brody (1978), the technique used in our experiments, which allows continuous measurement of renal blood flow in the rat and evaluates rapid changes in renal blood flow induced by direct intra-arterial drug administration to the kidney, makes it possible to evaluate, in anaesthetized rats, both the direct local renal action of 5-HT and the possible indirect actions induced by release of vasoconstrictor or vasodilator humoral agents, as has been suggested to occur with this agent in other animal species.

4.2. Vasoconstrictor renal effect of 5-HT and m-CPP

Local intra-arterial administration of 5-HT in intact animals, significantly increased perfusion pressure in a dose-dependent way. Our data are consistent with previous findings for isolated perfused kidney, after injections or infusions of 5-HT and 5-HTP (Stier et al., 1984, 1986).

The vasoconstriction obtained with all doses of 5-HT assayed was completely suppressed by pretreatment with ritanserin, a selective 5-HT_2 receptor antagonist (Awouters et al., 1988) and was reproduced by administration of similar doses of the 5-HT_2 receptor agonist, *m*-CPP (Humphrey et al., 1993), pointing to a higher selectivity of 5-HT_{2C} receptors (Hoyer et al., 1994). Similarly, the vasoconstrictor effect induced by *m*-CPP was blocked by the previous administration of ritanserin.

These results suggest that, in addition to the previously demonstrated central serotonergic mechanism (Zimmermann and Ganong, 1980; Alper and Ganong, 1984; Alper, 1990), there is a 5-HT receptor-mediated vasoconstrictor peripheral mechanism in the rat kidney that can be activated by exogenously administered 5-HT. These results are in agreement with the findings of other authors, who have proposed a 5-HT_2 receptor-mediated increase in renal vascular resistance for 5-HT receptor agonists in conscious rats (Zink et al., 1990; Lamiere et al., 1990), anaesthetized animals (Alper and Snider, 1987) and isolated perfused kidney preparations (Charlton et al., 1984; Janssen and Van Nueten, 1986, Tuncer and Vanhoutte, 1991). Nevertheless, the present results conflict with others describing both renal vasoconstriction and vasodilation for 5-HT (Shoji et al., 1989; Endlich et al., 1993). These differences can be attributed to differences between species or experimental models used, as proposed by Endlich et al. (1993). A 5-HT_2 receptor-mediated increase in renal vascular resistance after application of 5-HT has also been confirmed in anaesthetized as well as in conscious rabbits (Ikeda et al., 1987; Wright and Angus, 1987). More recently, however, contraction of the isolated renal artery of the rabbit has been found to be mediated by 5-HT_1-like receptors (Tadipatri et al., 1991).

4.3. Possible involvement of prostaglandin system and local release of renin or noradrenaline in the 5-HT vasoconstrictor effect

Since an interaction between 5-HT and the prostaglandin system has been reported for the isolated perfused rat kidney (Tuncer and Vanhoutte, 1991), hydronephrotic rat kidney (Endlich et al., 1993) and for dogs (Blackshear et al., 1986; Blackshear et al., 1991), we analyzed the effect of a cyclooxygenase inhibitor on the renal vasoconstrictor effects of 5-HT and *m*-CPP, using indomethacin at a dose commonly used to inhibit renal prostaglandin production (Roman and Kauker, 1978; Blackshear et al., 1986; Ding et al., 1989). In the light of our results, we propose that the 5-HT_2 receptor-mediated vasoconstriction is not dependent on an intact prostaglandin system. Our findings are consistent with results reported for the intact rat kidney by Ding et al. (1989) but contrast with other results obtained with dogs (Blackshear et al., 1986, 1991) and spontaneously hypertensive rats (Tuncer and Vanhoutte, 1991). Again, the complex mechanisms proposed to account for the renal 5-HT-prostaglandin interaction

explain the variability in the responses to 5-hydroxytryptamine reported for the renal blood supply.

The hemodynamic and renin responses to 5-HT receptor agonists vary greatly and depend on the receptor specificity of the drug under investigation (Alper and Ganong, 1984; Lorens and Van De Kar, 1987; Zink et al., 1990).

According to our experimental data, local release of renin induced through neuronal sympathetic mechanisms by 5-HT or *m*-CPP cannot be proposed because the β-adrenoceptor blockade by propranolol, which itself had no significant vascular effects in the in situ autoperfused rat kidney, did not block the renal vasoconstriction induced by both 5-HT and *m*-CPP. Moreover, pretreatment with indomethacin, a prostaglandin synthesis inhibitor used by others to show the involvement of a peripheral mechanism in renin release (Gerber et al., 1981), does not affect the vasoconstrictor effects of 5-HT or *m*-CPP.

A possible 5-HT- or *m*-CPP-induced release of NA from sympathetic nerve terminals cannot be proposed either. The α-adrenoceptor blockade elicited by prazosin had no effect on the renal vasoconstriction induced by these 5-HT receptor agonists. Moreover, at any of the doses employed neither 5-HT nor *m*-CPP modified the increases in perfusion pressure obtained at increasing stimulation rates of the renal sympathetic nerves.

4.4. Activation of renal angiotensin II induced by a 5-HT$_2$ mechanism

The abolition by enalapril of the generation of angiotensin II, which significantly reduces the pressor response to 5-HT and *m*-CPP, would imply involvement of the renin–angiotensin system in the vasoconstrictor effect obtained in the anaesthetized rat kidney. The present results are consistent with those reported for conscious rats by Alper (1990), who showed that the pressor response to 2,5-dimethoxy-4-iodoamphetamine (DOI), a selective 5-HT$_2$ receptor agonist, is substantially attenuated by the converting enzyme inhibitor, enalapril. In this sense, both DOI (the results of Alper, 1990) and *m*-CPP (according to our results) have effects different from those of quipazine, which produces hypertension that is not dependent on angiotensin II (Zink et al., 1990). The discrepancy between our results and those of Zink et al. (1990) may again be due to differences in the experimental conditions employed, i.e. the present experiments were performed in autoperfused rat kidney and 5-HT and *m*-CPP were injected i.a. in bolus form.

The dose-dependent inhibition by enalapril of the vasoconstrictor effect of 5-HT, together with the specificity of action of enalapril on the renal vascular reactivity of angiotensin I, but not of angiotensin II, confirm the ability of this 5-HT receptor agonist to activate the renin-angiotensin system. Additionally, the selective angiotensin II receptor antagonist, losartan, inhibited the vasoconstrictor effects of both angiotensin II and 5-HT. These results and the fact that ritanserin, a selective 5-HT$_2$ receptor antagonist, did not block the action of angiotensin II, show that 5-HT specifically activates 5-HT$_2$ receptors and that, on the renal vasculature, this activation induces an increase in angiotensin II formation able to activate the corresponding angiotensin II receptors and to increase perfusion pressure.

4.5. Conclusion

In conclusion, our data suggest that, in the vascular beds of the in situ autoperfused rat kidney, the vasoconstrictor serotonergic effect is mediated by local 5-HT$_2$ activation and by an increase in angiotensin II formation. In turn, this depends on activation of the converting angiotensin enzyme system but not on local release of renin through the prostaglandin system or sympathetic activation. However, whether these conflicting results reflect differences among species or whether they point to differences between the experimental models employed to determine the serotonergic mechanisms involved in renal blood flow, as has previously been proposed (Endlich et al., 1993), still remains to be elucidated.

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