SciMedCentral

JSM Renal Medicine

Mini Review

5-HT on Renal Vasculature: Vasodilator or Vasoconstrictor?

García-Pedraza JA[1,2], Morán A[1,2], Martín ML[1,2], and García-Domingo M[1,2,*]

[1]Department of Physiology and Pharmacology, University of Salamanca, Spain
[2]Biomedical Research Institute of Salamanca (IBSal), University Hospital of Salamanca-USAL-CSIC, Spain

*Corresponding author
García-Domingo M, Laboratory of Pharmacology, Department of Physiology and Pharmacology, Faculty of Pharmacy, Biomedical Research Institute of Salamanca (IBSal), University of Salamanca, 37007, Salamanca, Spain, Tel: 34-923-29-45-00; Fax: 34-923-29-45-15; Email: mgarciad@usal.es

Submitted: 16 February 2017

Accepted: 06 April 2017

Published: 08 April 2017

Keywords

- 5-Hydroxytriptamine
- Renal vascular tone
- Sarpogrelate
- 5-HT2 receptor
- Vasodilation
- Vasoconstriction

Abstract

The renal vasculature contributes to the cardiovascular homeostasis, regulating its vascular tone, blood flow as well as systemic blood pressure. The renovascular tone can be modulated by many vasoactive substances, highlighting 5-hydroxytryptamine (5-HT) which could exert totally opposite vascular effects in the kidney. This mini-review aims to determine if 5-HT predominantly acts as vasoconstrictor or vasodilator agent in the kidney.

To study modifications in the renal vasculature, one of the best experimental techniques *in vivo* is the *in situ* autoperfused rat kidney, which allows continuous measurement of rat renovascular resistance, permitting to evaluate rapid change in renal blood flow induced by i.e. drug administration. 5-HT directly exerts vasoconstrictor responses in the kidney of healthy rats, involving 5-HT_{2C} receptor activation. The induction of a pathological situation, such as hypertension or diabetes (where the kidney is predominantly at risk of injury), increases the serotonergic vasoconstrictor effect, but the receptor implicated is 5-HT_{2A}. This fact places 5-HT as an 'enemy' in the kidney, especially in renal disorders. Surprisingly, chronically blocking 5-HT_2 receptor with sarpogrelate makes 5-HT behave as a renal vasodilator agent by 5-$HT_{1/7}$ receptor activation. The modulation of the serotonergic system, leading to 5-HT renal vasodilation, opens new perspectives in the pharmacological approach to prevent/treat renal and cardiovascular pathologies.

ABBREVIATIONS

5-HT: 5-hydroxytrytamine; COX: cyclooxigenase; L-NAME: N(ω)-L-Arginine Methyl Ester.

INTRODUCTION

In the 19th century, Brodie showed how i.v. serum administration in cat caused a great variety of cardiac and vascular responses, underlining a potent vasoconstrictor effect in the kidney [1]. Some years later, it was determined that the substance responsible for that vasoconstriction was 5-hydroxytrytamine (5-HT), also called serotonin due to its main tonic action [2]. Although the pathophysiological role of 5-hydroxytrytamine is not yet fully understood because of the plethora of receptor type/subtypes described and the wide range of functions they mediate, it is well known that serotonin acts as neurotransmitter and local hormone at peripheral level [3,4], whose modulation permit obtain different pharmacological effects.

The complexity of 5-HT modulation at cardiovascular and renal levels has been widely studied *in vitro* and *in vivo*, but it has not yet been clearly defined due to the conflicting results obtained within different species and animal models [5-7]. Given that the contribution of renal vascular bed to the regulation of blood pressure is unarguably relevant because it influences on vascular homeostasis and systemic arterial pressure [8,9], the role of serotonergic system in the renal vasculature has become of great interest to design new pharmacological strategies to prevent/treat cardiovascular diseases. In this line, it is important to remark that *in vivo* models are usually characterized as more physiological (compared with *in vitro* models) since they allow to evaluate the mechanism of action of a drug, to investigate the effect in the organism as well as to study compensatory responses that occur in any living being.

Based on these premises, the purpose of this work is to review in detail how 5-hydroxytrytamine affects renal vascular tone *in vivo*, which are the 5-HT receptors involved and how different experimental conditions may modify the serotonergic influence, in order to evaluate possible pharmacological targets in several cardiovascular pathologies.

In vivo study of renal vascular tone

The vast majority of studies attempting to investigate the effects caused by serotonin within the renal vasculature utilize *in*

vitro techniques [7,10-12], probably due to the difficulty of using an *in vivo* model to study renal vascular bed, without affecting the ability of the kidney to regulate cardiovascular homeostasis. However, in 1978, Fink & Brody designed an *in vivo* experimental method, the *in situ* autoperfused rat kidney, to monitor changes in the renal perfusion pressure induced by i.e. administration of substances [13]. This technique represented a milestone in the procedure of investigating the renal vasculature, since it does not imply the dissection of any renal blood vessel or the kidney itself; in addition, this vascular bed receives the own sanguineous irrigation of the animal, with its corresponding perfusion pressure, without altering the capacity of the renal vasculature to autoregulate its blood flow and being able to respond to different vasoactive substances. Apart from that, this technique makes it feasible to assess, in anaesthetised rats, the possible indirect actions induced by the release of vasoconstrictor or vasodilator humoral agents.

Role of 5-HT in renal vascular bed in normal and pathological conditions

Morán et al. [20], have utilised the *in situ* autoperfused rat kidney technique to investigate how 5-HT can influence on renal vasculature modifying the renal vascular tone, as well as the possible role of indirect pathways in this regulation (vasoconstrictor or vasodilator agents). Thus, they have demonstrated that 5-HT directly exerts vasoconstrictor responses in the kidney of healthy rats; these vasoconstrictions are due to peripheral 5-HT_{2C} receptor activation, being mainly mediated through angiotensin II activation [14,15] (Table 1). Taking into account these outcomes, we assume that 5-HT is a relevant substance (a strong vasoconstrictor) in the regulation of kidney vascular tone, contributing to cardiovascular and renal homeostasis.

It is well known that the kidney is particularly at risk of damage from hypertensive and diabetic states. Both disorders powerfully contribute to worsening renal function, resulting in chronic kidney disease and end-stage renal disease [16,17]. Biomedical research is focused on the great variety of the pathogenic factors leading to renal impairment, highlighting the imbalance between constrictor and dilator substances; in this line, it has been evidenced an anomalous sensitivity of the whole vasculature to vasoconstrictor agents [18, 19], such as 5-HT. Considering that, the *in situ* autoperfused rat kidney allowed to evaluate vascular regulation by the kidney in a whole animal, using an experimental model of hypertension (induced by orally 21-day treatment with an inhibitor of the nitric oxide synthase, N(ω)-L-arginine methyl ester(L-NAME)), Morán et al. [20], indicated that in hypertensive rats 5-HT provoked a stronger vasoconstrictor effect in the kidney compared to normotensive rats. Surprisingly, the serotonergic receptor involved in these vasopressor actions changed compared to control animals, being 5-HT_{2A} the responsible receptor for this vasoconstriction (Table 1). These data are in agreement with other studies determining that 5-HT_{2A} receptor is the main route through which 5-HT exerts its deleterious actions at the cardiac and vascular levels in several cardiovascular pathologies [21,22], where the endothelial damage is a crucial factor in the higher responsiveness to serotonin [18,23].

Table 1: Summary of vascular effects of 5-hydroxytryptamine in the *in situ* auto perfused kidney of anesthetized rat.

Experimental model	5-HT pharmacological effect	Receptor involved	Indirect mechanism implicated
Healthy	Vasoconstriction	5-HT_{2C}	Angiotensin II
Hypertension		5-HT_{2A}	---------
Type 1 Diabetes		5-HT_{2A}	COX pathway
5-HT_2 blocker chronic treatment	Vasodilation	5-HT_{1B} 5-HT_{1D} 5-HT_7	NO pathway COX pathway ATP-K^+ channels

Abbreviations: ATP-K^+ channels; ATP-sensitive K^+ channels; COX: cyclooxygenase; NO: Nitric Oxide.

On the other hand, in diverse diabetes models (type I and type II) it has been demonstrated that the renal function is impaired, where the vascular contraction worsens the renal function. Restrepo et al. [24], using an type-I diabetes model induced by s.c.alloxan, showed that 5-HT induced vasopressor effects in the *in situ* autoperfused rat kidney, being the renal vasoconstriction higher than in normoglycaemic rats. As occurred in the hypertensive rats [20], the main receptor involved in such pressor effects was 5-HT_{2A} receptor, demonstrating, again, that this receptor subtype seems to be the more related to renal vasoconstrictor action in pathological state. In addition, the cyclooxygenase (COX) pathway activation was the main implicated in the vasopressor effect of 5-HT during diabetes [24] (Table 1).

May 5-HT pharmacological effect be changed?

Bearing in mind (i) the significant role of the 5-HT_2 receptors in the renovascular resistance in both control and cardiovascular pathological conditions, and (ii) that it has already been demonstrated that 5-HT_2 receptor blockade seems to offer multitude of benefits in cardiovascular and kidney disturbances, protecting against kidney diseases [21,22], García-Pedraza et al. [25], treated rats chronically with a selective 5-HT_2 receptor antagonist (sarpogrelate), studying whether the 5-HT behaviour at renal level changed when 5-HT_2 receptors were blocked. Curiously, the orally 14-day treatment with 30 mg/kg day of sarpogrelate induced a striking variation in the serotonergic effect on the renal vascular bed: 5-HT directly acted as a vasodilator agent in the *in situ* autoperfused rat kidney. Furthermore, the serotonergic receptors implicated in this renal vasodilation were 5-HT_{1B}, 5-HT_{1D} and 5-HT_7, involving the three main vasodilator pathways: nitric oxide, COX and ATP-sensitive K^+ channels, respectively (Table 1). These results clearly showed that modulating the serotonergic system could lead to beneficial effects in some renal diseases, where vasodilator actions would improve the renal functionality.

Therefore, considering all these review, we can say that 5-HT is a potent vasoconstrictor substance in the kidney; but, unexpectedly, using different pharmacological strategies, it may change its way of acting on renal vascular bed: going from a vasoconstriction due to 5-HT_2 activation to a vasodilation by 5-$HT_{1/7}$ activation.

Perspectives

Admittedly, there are still some gaps that should be addressed for future investigations:

What does 5-HT$_2$ receptor blockade originate in animals with renal damage? It is worth to say that *in vitro* studies by García-Pedraza et al. [26], suggest that blocking selectively 5-HT$_2$ serotonergic receptor (with sarpogrelate) significantly improves endothelial function, alleviates the development of hypertension, renal hypertrophy and reduces oxidative stress during diabetes. Nevertheless, up to now, neither these authors nor others have analyzed whether 5-HT$_2$-antagonist treatment may modulate serotonergic system at vascular renal level in *in vivo* experimental models with kidney damage, such as hypertension or diabetes.

What would it happen if we selectively block a 5-HT$_2$ receptor subtype? As described by Morán et al. [14,15,20], and Restrepo et al. [24], the main receptor subtypes involved in renal vasoconstriction are 5-HT$_{2C}$ and 5-HT$_{2A}$. It would be a great insight in this field to perform studies specifically and chronically blocking 5-HT$_{2A}$ or 5-HT$_{2C}$ receptor subtype. This fact would clarify and help to find a new specific therapeutic approach.

Consequently, is 5-HT a friend or foe in the renal vasculature? In vivo studies show 5-HT as a strong vasopressor agent, enhancing its constrictor role in cardiovascular pathologies; however, these authors also demonstrate that it is possible to act on the serotonergic system unmasking the "desired" vascular effects (i.e. vasodilation), which would be a useful strategy in kidney disturbances. Therefore, 5-HT is placed within the potentially adaptable systems to jam cardiovascular adverse effects and potentiate the beneficial ones.

CONCLUSION

This review shows that serotonin predominantly behaves as a vasoconstrictor agent at renal level mainly by activation of 5-HT$_2$ receptor; however, the 5-HT receptor subtype involved depends on the pathophysiological state. Surprisingly, it is brought to light that selective 5-HT$_2$ receptor blockade makes 5-HT behave as renal vasodilator agent.

The discovery of the ability of serotonergic system to modulate itself sheds needed light on the complexity of 5-HT to regulate renal blood flow, and consequently systemic pressure. To consider 5-HT$_2$ receptor blockade as a therapeutic target in cardiovascular disorders, it is needed to understand the pharmacological profile of serotonin in those conditions, and these authors add to this understanding.

REFERENCES

1. Brodie TG. The immediate action of an intravenous injection of blood-serum. J Physiol. 1900; 26: 48-71.
2. Rapport MM, Green AA, Page IH. Serum vasoconstrictor (serotonin). IV. Isolation and characterization. J Biol Chem. 1948; 176: 1243-1251.
3. Ramage AG, Villalón CM. 5-Hydroxytryptamine and cardiovascular regulation. Trends Pharmacol Sci. 2008; 29: 472-481.
4. Ayme-Dietrich E, Aubertin-Kirch G, Maroteaux L, Monassier L. Cardiovascular remodeling and the peripheral serotonergic system. Arch Cardiovasc Dis. 2017; 110: 51-59.
5. Shoji T, Tamaki T, Fukui K, Iwao H, Abe Y. Renal hemodynamic responses to 5-hydroxytryptamine (5-HT): involvement of the 5-HT receptor subtypes in the canine kidney. Eur J Pharmacol. 1989; 171: 219-228.
6. Tian RX, Kimura S, Kondou N, Fujisawa Y, Zhou MS, Yoneyama H, et al. DOI, a 5-HT2 receptor agonist, induces renal vasodilation via nitric oxide in anesthetized dogs. Eur J Pharmacol. 2002; 437: 79-84.
7. Watts SW, Thompson JM. Characterization of the contractile 5-hydroxytryptamine receptor in the renal artery of the normotensive rat. J Pharmacol ExpTher. 2004; 309: 165-172.
8. Lamas S, Rodríguez-Puyol D. Endothelial control of vasomotor tone: the kidney perspectives. SeminNephrol. 2012; 32: 156-166.
9. Thomas P, Dasgupta I. The role of the kidney and the sympathetic nervous system in hypertension. Pediatr Nephrol. 2015; 30: 549-560.
10. Greene EL, Houghton O, Collinsworth G, Garnovskaya MN, Nagai T, Sajjad T, et al. 5-HT(2A) receptors stimulate mitogen-activated protein kinase via H(2)O(2) generation in rat renal mesangial cells. Am J Physiol Renal Physiol. 2000; 278: F650-F658.
11. Hill PB, Dora KA, Hughes AD, Garland CJ. The involvement of intracellular Ca(2+) in 5-HT(1B/1D) receptor-mediated contraction of the rabbit isolated renal artery. Br J Pharmacol. 2000; 130: 835-842.
12. Hinton JM, Hill P, Jeremy J, Garland C. Signalling pathways activated by 5-HT(1B)/5-HT(1D) receptors in native smooth muscle and primary cultures of rabbit renal artery smooth muscle cells. J Vasc Res. 2000; 37: 457-468.
13. Fink GD, Brody MJ. Continuous measurement of renal blood flow changes to renal nerve stimulation and intra-arterial drug administration in rat. Am J Physiol. 1978; 234: H219-H222.
14. Morán A, Velasco C, Martín ML, San Román L. Renal vasoconstrictor response to 5-hydroxytryptamine in the *in situ* autoperfused rat kidney: involvement of angiotensin II and the 5-HT2 receptor activation. Eur J Pharmacol. 1997; 330: 205-211.
15. Morán A, Ortiz de Urbina AV, Martín ML, García M, Rodríguez-Barbero A, Dorado F, et al. Characterization of contractile 5-hydroxytryptamine receptor subtypes in the *in situ* autoperfused kidney in the anaesthetized rat. Eur J Pharmacol. 2008; 592: 133-137.
16. Bjornstad P, Cherney D, Maahs DM. Early diabetic nephropathy in type 1 diabetes: new insights. Curr Opin Endocrinol Diabetes Obes. 2014; 21: 279-286.
17. Elsherbiny NM, Al-Gayyar MM. The role of IL-18 in type 1 diabetic nephropathy: The problem and future treatment. Cytokine. 2016; 81:15-22.
18. Miranda FJ, Alabadí JA, Lloréns S, Ruiz de Apodaca RF, Centeno JM, Alborch E. Experimental diabetes induces hyperreactivity of rabbit renal artery to 5-hydroxytryptamine. Eur J Pharmacol. 2002; 439: 121-127.
19. Hao CM, Breyer MD. Physiological regulation of prostaglandins in the kidney. Annu Rev Physiol. 2008; 70: 357-377.
20. Morán A, Ortiz de Urbina AV, Martín ML, Rodríguez-Barbero A, Román LS. Characterization of the contractile 5-hydroxytryptamine receptor in the autoperfused kidney of L-NAME hypertensive rats. Eur J Pharmacol. 2009; 620: 90-96.
21. Doggrell SA. Sarpogrelate: cardiovascular and renal clinical potential. Expert Opin Investig Drugs. 2004; 13: 865-874.
22. Saini HK, Takeda N, Goyal RK, Kumamoto H, Arneja AS, Dhalla NS. Therapeutic potentials of sarpogrelate in cardiovascular disease. Cardiovasc Drug Rev. 2004; 22: 27-54.

23. Miranda FJ, Alabadí JA, Lloréns S, Ruiz de Apodaca RF, Centeno JM, Alborch E. Diabetes-induced changes in endothelial mechanisms implicated in rabbit carotid arterial response to 5-hydroxytryptamine. Eur J Pharmacol. 2000; 401: 397-402.

24. Restrepo B, García M, Rodríguez-Barbero A, Román LS, Martin ML, Morán A. Participation of cyclooxygenase pathway in the vasoconstriction induced by 5-HT in the *in situ* autoperfused kidney of long-term diabetic rats.Eur J Pharmacol. 2011; 659: 37-44.

25. García-Pedraza JA, García M, Martín ML, Rodríguez-Barbero A, Morán A. 5-HT2 receptor blockade exhibits 5-HT vasodilator effects via nitric oxide, prostacyclin and ATP-sensitive potassium channels in rat renal vasculature. Vascul Pharmacol. 2016; 79: 51-59.

26. García-Pedraza JÁ, Ferreira-Santos P, Aparicio R, Montero MJ, Morán A. Blocking 5-HT2 receptor restores cardiovascular disorders in type 1 experimental diabetes. Sci Rep. 2016; 6: 33979.

Cite this article

García-Pedraza JA, Morán A, Martín ML, Domingo MG (2017) 5-HT on Renal Vasculature: Vasodilator or Vasoconstrictor? JSM Renal Med 2(1): 1008.