5-HT on Renal Vasculature: Vasodilator or Vasoconstrictor?

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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-HT1 receptors. 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-HT2C. This fact places 5-HT as an ‘enemy’ in the kidney, especially in renal disorders. Surprisingly, chronically blocking 5-HT2C receptor with sarpogrelate makes 5-HT behave as a renal vasodilator agent by 5-HT1A 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-hydroxytryptamine; COX: cyclooxygenase; 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-hydroxytryptamine (5-HT), also called serotonin due to its main tonic action [2]. Although the pathophysiological role of 5-hydroxytryptamine 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-hydroxytryptamine 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...
Considering that, the vasculature to vasoconstrictor agents [18, 19], such as 5-HT, pathogenic factors leading to renal impairment, highlighting the relevant substance (a strong vasoconstrictor) in the regulation homeostasis.

Taking into account these outcomes, we assume that 5-HT is a mediated through angiotensin II activation [14,15] (Table 1). Demonstrated that 5-HT directly exerts vasoconstrictor (vasoconstrictor or vasodilator agents). Thus, they have as the possible role of indirect pathways in this regulation renal vasculature modifying the renal vascular tone, as well.

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-HT2C 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 hypertension 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 powerfully contribute to worsening renal function, resulting in normotensive rats. Surprisingly, the serotonergic receptor involved in these 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.

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

<table>
<thead>
<tr>
<th>Experimental model</th>
<th>5-HT pharmacological effect</th>
<th>Receptor involved</th>
<th>Indirect mechanism implicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>Vasoconstriction</td>
<td>5-HT2C</td>
<td>Angiotensin II</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>5-HT2A</td>
<td>Angiotensin II</td>
</tr>
<tr>
<td>Type 1 Diabetes</td>
<td></td>
<td>5-HT2A</td>
<td>COX pathway</td>
</tr>
<tr>
<td>5-HT, blocker chronic treatment</td>
<td>Vasoconstriction</td>
<td>5-HT2, 5-HT1D, 5-HT1C</td>
<td>NO pathway, COX pathway, ATP-K+ channels</td>
</tr>
</tbody>
</table>

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

May 5-HT pharmacological effect be changed?

Bearing in mind (i) the significant role of the 5-HT2 receptors in the renovascular resistance in both control and cardiovascular pathological conditions, and (ii) that it has already been demonstrated that 5-HT2 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-HT2 receptor antagonist (sarpogrelate), studying whether the 5-HT behaviour at renal level changed when 5-HT2 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-HT1D, 5-HT1A and 5-HT2A, 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 action on renal vascular bed: going from a vasoconstriction due to 5-HT2 activation to a vasodilation by 5-HT1D activation.
Perspectives

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

*What does 5-HT 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-HT₂ 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-HT₂-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-HT₂ 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-HT₂A, and 5-HT₂C. It would be a great insight in this field to perform studies specifically and chronically blocking 5-HT₂A or 5-HT₂C 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 *in vivo* studies show 5-HT as a strong vasoconstrictor 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-HT₂ receptor; however, the 5-HT receptor subtype involved depends on the pathophysiological state. Surprisingly, it is brought to light that selective 5-HT₂ 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-HT₂ 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**


