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School of Pharmacy & Pharmaceutical Sciences
Isfahan University of Medical Sciences

Short Communication

Renal vascular response to angiotensin 1-7 in rats: the role of Mas receptor

Mehdi Nematbakhsh[1,2,*] and Azam Mansouri[2]

[1]*Water and Electrolytes Research Center, Isfahan University of Medical Sciences, Isfahan, I.R. Iran.*
[2]*Department of Physiology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, I.R. Iran.*

Abstract

Recently a cross talk between angiotensin 1-7 (Ang1-7) receptor (MasR) and angiotensin II receptors types 1 and 2 (AT1R and AT2R) has been highlighted. The effects of MasR antagonist (A779) compared to the vehicle on the renal blood flow (RBF) and renal vascular resistance (RVR) responses to Ang1-7 (300 ng/kg/min) infusion in the absence of Ang II receptors in male and female rats were determined at controlled renal perfusion pressure. Ang1-7 infusion did not alter mean arterial pressure in male and female rats. However, A779 compared to vehicle increased RBF (18% *vs* 3%) and decreased RVR (13% *vs* 4%) responses to Ang1-7 infusion significantly ($P < 0.05$) in male when AngII receptors were blocked. Such observation was not occurred in female animals. Finally it was concluded that renal vascular responses to Ang1-7 administration may not be exerted by MasR in male rats, and these responses are not mediated with AngII receptors.

Keywords: Angtensin1-7; Angiotensin II receptors; Mas receptor; Gender; Rat

INTRODUCTION

There are evidences that renal diseases and function of renin angiotensin system (RAS) in kidneys are gender related (1-3). The major product of RAS is angiotensin II (AngII) which acts via AngII receptors type 1 and 2 (AT1R, AT2R). Angiotensin 1-7 (Ang1-7) is another component of RAS that its physiological and pharmacological actions are assumed to be exerted via a specific receptor called Mas receptor (MasR) which is considered as AT1R antagonist (4). Possible interactions between AngII and MasR are existed (5), and previously we reported that by co-blocking of AngII receptors, the role of MasR in pressure natriuresis and diuresis was highlighted in male rats (6). In addition, some actions of Ang1-7 also may be altered by co-blockades of AT1R and AT2R (7,8).

The renal expression of MasR in female is different from male (9). In general, the Ang 1-7 actions are expected to be exerted via MasR, however in some experimental model the renal blood flow (RBF) response to Ang 1-7 infusion was reported to be higher when MasR was blocked (10,11), and therefore Ang1-7 may act through different pathway other than MasR. It is hypothesized that when AT1R and AT2R are blocked, RBF and renal vascular resistance (RVR) responses to Ang1-7 are altered gender dependently, and these responses are not limited by MasR antagonist (A779).

MATERIALS AND METHODS

This study was designed based on our previous study (5,6). Male (n = 12, 198.2 ± 5.37 g) and female (n = 18, 185.9 ± 1.6 g) Wistar rats were anaesthetized (Inactin, 175 mg kg^{-1} i.p. Sigma, St Louis, MO, USA.), and air ventilation was facilitated by tube insertion into the trachea. Polyethylene catheters were inserted into the jugular vein, carotid artery and femoral arteries. Renal perfusion pressure (RPP) was measured via femoral artery, and it was controlled by an adjustable clamp placed around the aorta above the level of the renal arteries.

*Corresponding author: M. Nematbakhsh
Tel/Fax : +98-3137929019
Email: nematbakhsh@med.mui.ac.ir

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The left kidney was gently placed in a stable cup, and the flow probe was placed around the renal artery to obtain renal blood flow (RBF). The RBF was measured by a transit-time ultrasound flowmetry (Transonic Systems, Ithaca, NY, USA.). The animals were monitored for about 30 min before antagonist infusion, and this time was considered as equilibration period.

After equilibration period, the antagonists (or vehicle) were administrated via jugular vein by micro-infusion pumps (New Era Pump System Inc. Farmingdale, USA) through the experiment. The rats randomly assigned in 4 groups of experiments as followings:

Group1, male rats simultaneously received MasR (A779), AT1R (losartan), and AT2R (PD123319) antagonists; Group 2, male rats received the same regimen as group 1 except vehicle instead A779; Groups 3 and 4, female rats treated as groups 1 and 2, respectively.

Losartan was from Darou Pakhsh Pharma Co. (Tehran, Iran), PD123319 from Sigma, St. Louis (MO, USA), and A779 from Bachem Bioscience Inc. (King of Prussia, PA, USA). Losartan, PD123319, and A779 were administrated as 10 mg/kg bolus plus 10 mg/kg.h, 1 mg/kg bolus plus 1 mg/kg.h, and 50 µg/kg bolus plus 50 µg/kg.h, respectively. All the animals received antagonist (or vehicle) 90 min before Ang1-7 infusion was commenced. Mean arterial pressure (MAP), RPP and RBF were continually measured during the experiment. MAP, RPP and RBF measurements at 90 min post antagonists (or vehicle) infusion were considered as the baseline (control) measurement for Ang1-7 infusion phase. Then, all the animals received Ang1-7 (300 ng/kg/min) for period of 30 min at controlled RPP.

The RPP was controlled as baseline measurement during Ang1-7 administration. The last 2-3 min of Ang1-7 infusion was considered as the measurement. Finally, the animals were sacrificed humanely; the left kidney was removed immediately and weighed. Renal vascular resistance (RVR) was calculated as RPP/RBF ratio.

Data are expressed as mean ± S.E.M. ANOVA for repeated measures data was used to compare each parameter between the groups. The P values ≤ 0.05 were considered statistically significant.

RESULTS

Data analyses indicated that administration of Ang1-7 did not alter MAP (male: $P_{time} = 0.2$, $P_{group} = 0.1$, $P_{time \times group} = 0.4$; female: $P_{time} = 0.3$, $P_{group} = 0.4$, $P_{time \times group} = 0.5$) and RPP (male: $P_{time} = 0.2$, $P_{group} = 0.1$, $P_{time \times group} = 0.9$; female: $P_{time} = 0.2$, $P_{group} = 0.6$, $P_{time \times group} = 0.4$) when compared with baseline (control) measurement in both genders (Fig. 1).

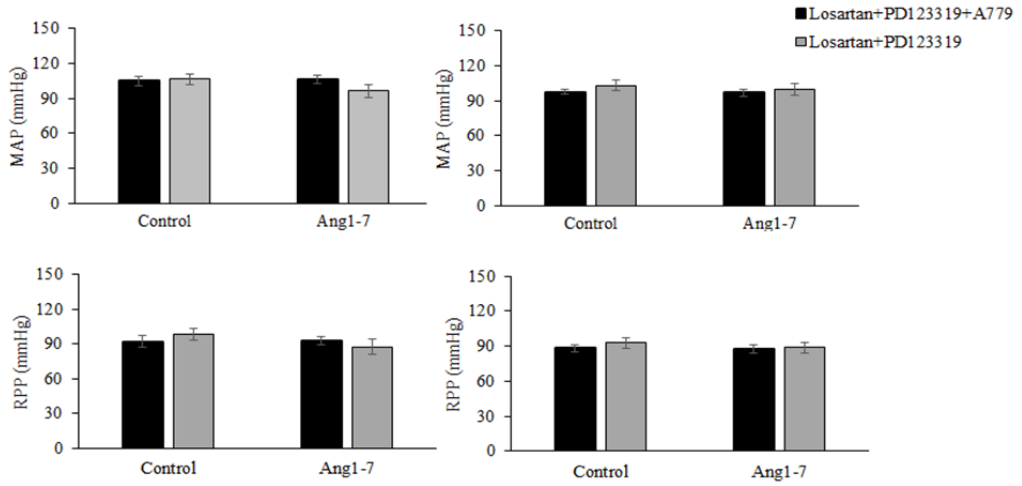

Fig. 1. Mean arterial pressure (MAP) and renal perfusion pressure (RPP) at 90 min post antagonists (or vehicle) administration (control), and 30 min post Angiotensin 1-7 infusion (Ang1-7) in male (left panel) and female (right panel) rats. Statistical analysis was performed using ANOVA for repeated measured data (see the text for analyses). P values ≤ 0.05 was considered significant. (n = 6 in each male group and n = 9 in each female group).

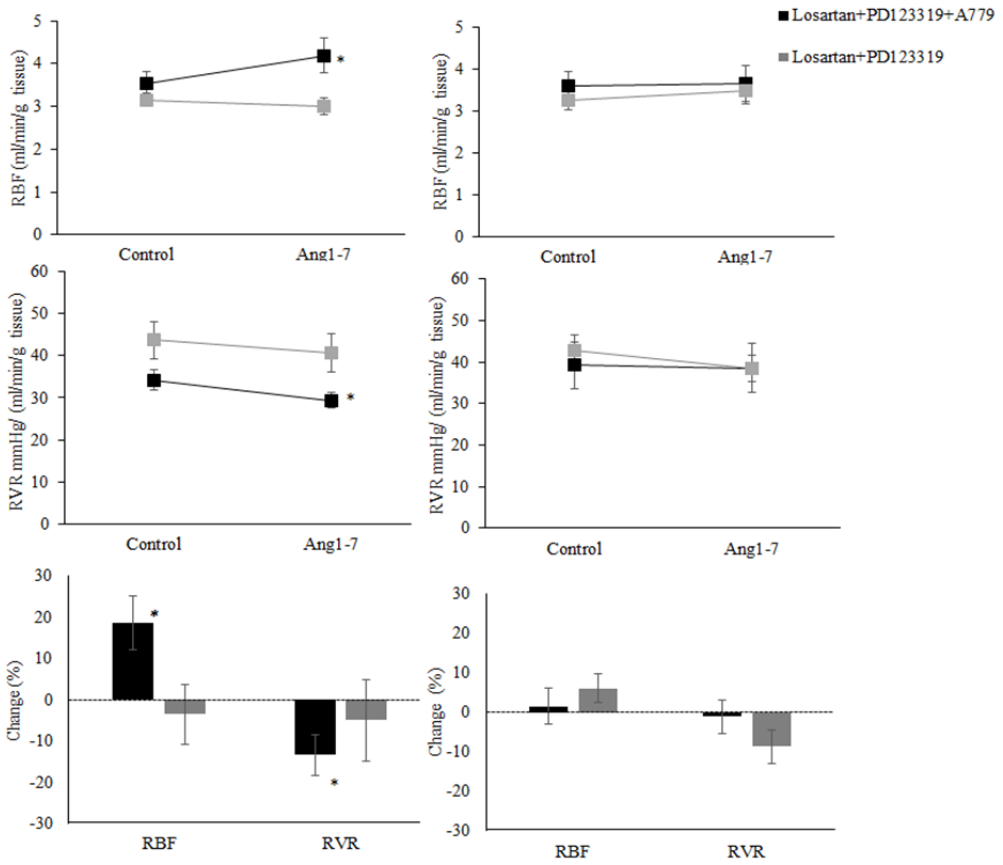

Fig. 2. Renal blood flow (RBF) and renal vascular resistance (RVR) responses to angiotensin1-7 (Ang1-7) infusion. 90 min post antagonists (or vehicle) administration (control), and 30 min post Ang1-7 infusion in male (left panel) and female (right panel) rats. Statistical analysis was performed using ANOVA for repeated measured data (see the text for analyses). *Indicates significant difference from other group, and *P* values ≤ 0.05 was considered significant. (n = 6 in each male group and n = 9 in each female group).

Ang1-7 administration caused an increase in RBF by 18% (from 3.52 ± 0.28 to 4.19 ± 0.40 mL/min/g tissue) and a decrease in RVR by 13% (from 34.22 ± 2.48 to 29.36 ±1.79 mmHg/mL/min/g tissue) in male rats when all three receptors were blocked (group 1), and they were significantly different when compared with male rats when AT1R and AT2R were blocked alone (group 2), (RBF; $P_{time} = 0.1$, $P_{group} = 0.04$, $P_{time \times group} = 0.03$; RVR: $P_{time} = 0.1$, $P_{group} = 0.04$, $P_{time \times group} = 0.7$) as shown in Fig. 2. The significant difference ($P < 0.05$) in RBF and RVR between the groups 1 and 2 reveals the important role of MasR blockade after Ang1-7 infusion in male rats (Fig. 2). On the contrary, no significant differences in RBF ($P_{time} = 0.1$, $P_{group} = 0.6$, $P_{time \times group} = 0.5$) and RVR ($P_{time} = 0.2$, $P_{group} = 0.8$, $P_{time \times group} = 0.3$) were observed in female rats when all three receptors were blocked (groups 3) compared with the rats when AT1R and AT2R were blocked alone (group 4). .

DISCUSSION

The major finding of this study indicated that RBF response to Ang1-7 infusion was increased significantly in male rats when AT1R, AT2R and MasR were blocked compared to condition that AT1R and AT2R alone were blocked. This finding highlights the significant role of MasR blockade in male rats. The effects of Ang1-7 such as natriuresis, diuresis, and vasodilation are exerted via MasR (12), however, when AT1R and AT2R also were blocked different result may be obtained. Generally, once MasR is blocked, the action of Ang1-7 is expected to fail, however, our result provided significant effect in RBF response to Ang1-7 infusion in male when MasR, AT1R and AT2R were blocked.

This finding indicates that Ang1-7 may also exert its physiological and pharmacological effects through other pathways other than MasR. Other experimental studies in estradiol-treated ovariectomazied rats support this hypothesis that RBF response to Ang1-7 infusion was found to be higher when MasR was blocked by A779 (10, 11). Although it is known that Ang 1-7 exerts a vasodilator effect via MasR, but the potentiation of bradykinin is another possible pathway that is exerted by Ang1-7 (13). Indeed, Ang 1-7 binds to angiotensin converting enzyme (ACE) and the possible crosstalk between ACE and bradykinin B2 receptor occurs (14). On the other hand, there are some differences in male and female genetic polymorphisms related to ACE and ACE2 (15), thus possibly the ACE polymorphism is involved to potentiate bradykinin by Ang 1-7 differently in male and female. Worthwhile to mention that in our study the RPP was measured from femoral artery while femoral artery pressure is not exactly equal to RPP due to vascular resistance alteration. This negligible difference, however, could be ignored.

CONCLUSION

It is concluded that renal vascular response to Ang1-7 may not be exerted by MasR completely. The other pathways not mediated by AT1R and AT2R may be involved.

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