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BIOLOGICAL EVALUATION OF A NOVEL ANGIOTENSIN II RECEPTOR ANTAGONIST AS AN ANTI-HYPERTENSIVE DRUG

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A compound **1a** was synthesized by our research group. Affinities to Ang II (AT_1) receptor in vitro experiments suggested that **1a** displayed an IC_{50} value of 2.43 ± 0.79 nM, Ki value of 1.58 ± 0.25 nM. The maximum depressurization value at 10 mg/kg displayed 43.52 ± 2.09 mmHg in spontaneously hypertensive rats. The experimental results demonstrated that **1a** had high-efficiency, long-acting antihypertensive activity, which was worthy of further study for new drug development.

Keywords: Anti-hypertension, AT_1 receptor antagonist, ARBs

1. INTRODUCTION

Hypertension or high blood pressure, is a long-term medical condition in which is systolic blood pressure ≥140mmHg (18.6kPa) and/or diastolic blood pressure ≥90mmHg (12kPa). It rarely has noticeable symptoms, but if untreated, it increases risk of serious problems such as heart attacks and strokes (Lewington et al., 2002). The renin-angiotensin-system (RAS) plays an important role in regulating blood pressure. Angiotensin II receptor antagonists are currently novel antihypertensive drugs. There are four subtypes of angiotensin II receptors, namely AT_1, AT_2, AT_3, and AT_4. Most of the known regulation of human blood pressure effects of angiotensin II are mediated through stimulation of the AT_1 receptor.
In present study we observed the compound **1a** had an efficient to AT_1 receptor and anti-hypertensive activity in spontaneously hypertensive rats (SHRs).

2. EXPERIMENTAL MATERIALS AND METHODS

The compound **1a** was designed and synthesized in our group. Vascular smooth muscle cells (VSMCs), bovine serum albumin (BSA), and angiotensin II were purchased from Zhongshan Hospital, Shanghai. Losartan was obtained from Shanghai Zhong Kang Wei Ye Biological Technology Co., Ltd. The oleic acid and DMSO were purchased from Sinopharm Chemical Reagent Co., Ltd. The non-linear regression program Graph Pad Prism 7 software was obtained from Network of Science Software of China.

2.1. Affinities to Ang II (AT_1) receptor in vitro

The vascular smooth muscle cells (VSMCs) were isolated from thoracic aorta of SD rats and cultured in 3-4 days for the experiments (Marks A. R 2003). The **1a** compound and losartan were dissolved in DMSO and diluted with PBS before the experiments. Sar1, Ile8– angiotensin II (Shanghai First people's Hospital, Shanghai, China) was used in this assay. 0.1 nM ^{125}I- Ang II and compounds of different concentrations were maintained in all samples when the cells adhered to the wall. Then they were cultivated at 4 ℃ for 150 min. Nonspeciphic binding was measured in the presence of 1 nM

Ang II. Cells bound by ^{125}I-Ang II were counted by g-counter (SN-682, Rihuan Company, Shanghai). The IC_{50} value was estimated by the linear portion of the competition curves.

2.2. Antihypertensive activity in SHRs

Spontaneously hypertensive rats (250±30g) were purchased from Beijing Experimental Animal Technology Co. Ltd. All experiments were approved by the Institutional Animal Care and Use Committee of the Institute of Health Sciences, Shanghai Institutes for Biological Sciences of Chinese Academy of Sciences. We used non-invasive method to measure SBP and SDP in SHRs (250±30 g) under conscious conditions. The drug was dissolve in mixed solution of oleic acid and DMSO (V_1: V_2 = 4:1) at 10 mg/kg. The SBP and SDP were measured in different three SHRs for **1a** which were recorded at 0 h (not administered) and 1-12 h, 24 h after administration (Xiaolu Bao et al., 2015). The mean blood pressure (MBP) was calculated by this formula: MBP = (SBP-DBP)/3 + DBP.

3. RESULT ANALYSIS

3.1. Radioactive receptor binding assay data analysis

The radioligand binding experiments showed that the compound **1a** had strong affinity with the AT_1 receptor, and the affinity was stronger than the positive control Losartan.
Compound **1a** had an IC_{50} value of 2.43 ± 0.79 nM, Ki value of 1.58 ± 0.25 nM, as shown in Table.

Table1: IC_{50} and Ki value of the compound **1a** and Losartan

Compound	IC_{50} ± SEM (nM)	Ki (nM)
1a	2.43 ± 0.79	1.58 ± 0.25
Losartan	12.19 ± 0.37	8.23 ± 0.27

3.2 Antihypertensive activity of 1a in SHRs

1a could significantly reduce blood pressure after entering to SHRs body. And it has a quick onset, stable blood pressure, and reaches the maximum decompression value 5 h after administration. The maximum depressurization value at 10 mg/kg was 43.52 ± 2.09 mmHg, which was weaker than the positive controls Losartan (Weibo Zhu et al., 2016).

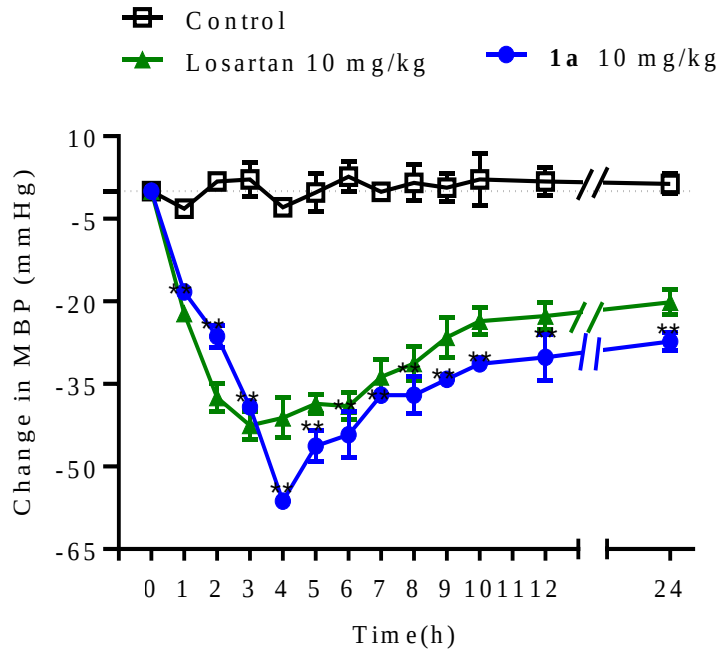

Fig. Effect of **1a** on MBP of SHRs (*P<0.05, **P<0.01 VS Control)

3. DISCUSSION AND CONCLUSION

The compound **1a** has strong affinity for AT_1 receptors which signnificantly decreases blood pressure of SHRs. Thus, **1a** has an antihypertensive activity to develop a new anti-hypertension drug in the future.

4. ACKNOWLEDGEMENTS

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