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Olmesartan medoxomil reverses left ventricle hypertrophy and reduces inflammatory cytokine IL-6 in the renovascular hypertensive rats

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Abstract. – AIM: To investigate the effects of Olmesartan Medoxomil (OM) on left ventricle hypertrophy (LVH) and inflammatory cytokines IL-6 and IL-10 levels in renovascular hypertensive rats.

MATERIALS AND METHODS: Qualified 30 male Wistar rats were randomly divided into three groups: sham-operation group (SO, n=10), model control group (MC, n=10), and Olmesartan Medoxomil group (OM, n=10). Renovascular hypertension was induced by ligating the abdominal aorta and 10 mg/kg OM was administered daily to the OM group by gastric perfusion for 7 weeks. The ratio of left ventricle mass to body weight (LVM/BW) was calculated as the index of cardiac hypertrophy, and the inflammatory cytokines IL-6 and IL-10 in serum and cardiac tissue were measured by ELISA assays.

RESULTS: The LVM/BW ratios in the MC group were about 50% higher than that in the SO group ($p < 0.001$). The OM group showed much reduced LVM/BW ratios compared with the MC group ($p < 0.001$) and were similar to that in the SO group ($p > 0.05$), indicating a complete reversal of the left ventricular hypertrophy caused by aorta ligation. The IL-6 and IL-10 levels in both the serum and cardiac tissue increased following aorta ligation (MC vs. SO, $p < 0.001$). While OM treatment significantly reduced IL-6 levels in the aorta-ligated rats (OM vs. MC, $p < 0.001$), IL-10 levels were not affected (OM vs. MC, $p > 0.05$).

CONCLUSIONS: OM completely reversed left ventricle hypertrophy and reduced IL-6 levels in renovascular hypertensive rats. Its effect on IL-10 levels in this animal model was not statistically significant.

Key Words:
Olmesartan Medoxomil, Left ventricle hypertrophy, Renovascular hypertension, IL-6, IL-10.

Introduction

Hypertension is one of the most prevalent diseases and a major health problem worldwide affecting about 20% of the adult population in many countries[1]. It often proceeds the development of atherosclerosis, coronary heart disease, and cerebro-vascular diseases[2]. Yet hypertension is the major cause of LVH. LVH is related with a greater risk of hypertensive complications[3,4], and the presence of LVH increase mortality of cardiovascular disease[4-6]. According to statistics[7], there are 20%-40% hypertensive patients with complication of LVH. Recent data have demonstrated a strong association between hypertension and inflammatory process[8,9].

In normotensive males and females, elevated plasma CRP levels were found to be significantly associated with an increased risk of future development of hypertension, suggesting that hypertension is an inflammatory disorder[10]. More and more researches show that pro-inflammatory cytokines play a key role in the pathogenesis and development of hypertension[11,12], such as IL-6. IL-6 is an inflammatory cytokine, it can result in hypertensive heart disease[10,13,14] and plays a part in fighting infection. On the contrary, IL-10 is an anti-inflammatory cytokine, which has manifested protective effects in animal and clinical studies[15]. IL-10 is a pleiotropic cytokine, and it exhibits effect in immunoregulation and inflammation.

Olmesartan medoxomil is a highly selective non-peptide angiotensin II receptor antagonist[16,17], and it is used for the treatment of hypertension[18]. It has also been revealed that angiotensin II receptor blockers (ARBs) have effects of lowering blood pressure, including decrease of IL-6[19], but its effects on IL-10 is seldom reported. Likewise, cross-sectional studies have shown that IL-6 are elevated in patients with essential hypertension[8].

As OM exhibits highly potent and selective affinity for angiotensin II type 1 receptor[20], and LVH is related with high mortality in essential hypertension patients[21]. Little is known, the ef-

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fects of OM on LVH and the levels of inflammatory cytokines, therefore, we detect IL-6 and IL-10 levels in renovascular hypertensive rats, in order to offer new thoughts for diagnosis and therapy to hypertension.

Materials and Methods

Materials

Two month old Wistar rats (n=30) weighed about 170-250 g were purchased from Laboratory Animal Center of Shandong Lüye Pharmaceutical Co. Ltd, China. IL-6 and IL-10 reagent kits were purchased from Wuhan Beinglay Biotechnology Co. Ltd, China.

Preparation of Animal Model

Renovascular hypertension was induced by ligating the abdominal aorta in healthy Wistar rats. Rats were anesthetized with 10% Chloral hydrate (0.3 ml/100 g, ip). The skin was incised, subcutaneous tissue separated, and the abdominal cavity opened to expose the abdominal aorta (AA) and left and right renal arteries. Once the arteries were isolated, a suture line was put around the site of AA above where the left and right renal arteries branched off and the vessel was ligated with a 5th needle (the vascular coarctation must be reached to more than 50% degree). The needle was subsequently removed and the abdomen cavity closed. In sham-operated rats, sutures were put under the artery but not tied. All rats received penicillin daily (100,000 units) after operation for three days and were fed normally.

Group Assignment and Drug Administration

Thirty rats were randomized into three groups (10 in each group): sham-operation group (SO), model-control group (MC), and Olmesartan Medoxomil group (OM). On the third day after operation, all rats in the OM group received daily OM administration (10 mg/kg) by gastric perfusion for 7 weeks, and the other two groups were given sterilized water instead.

Left Ventricle Mass Measurement and Sample Collection

Rats were weighed and anesthetized with 10% Chloral hydrate (0.3 ml/100 g, ip). The left ventricle mass was measured with a two-dimensional (2D) echocardiographic recording system (Philips IE33) operated by the same technician through the entire study. Each sample was measured three times, and the ratio of the average left ventricle mass to body weight (LVM/BW) was calculated as the index of cardiac hypertrophy. At the end of the study, all rats were killed, and blood samples were collected from aorta. Sera were separated and stored at –80°C. The levels of IL-6 and IL-10 were determined by enzyme linked immunoassays (ELISA).

Statistical Analysis

The data were expressed in the form and comparison among groups was analyzed by one-way ANOVA. Differences with p value less than 0.05 were considered statistically significant. All statistical analyses were performed with SPSS software version 13.0 (SPSS Inc., Chicago, IL, USA).

Results

After 7 weeks of treatment, the number of survived rats and the ratio of left ventricle mass to body weight (LVM/BW) of each group are showed in Table I. Rats in MC group had serious cardiac hypertrophy, and OM had significant effects on attenuating the left ventricular hypertrophy.

As demonstrated in Table II, the levels of IL-6 and IL-10 increased significantly in MC by comparison to SO group. While attenuating the cardiac hypertrophy, the levels of IL-6 in serum and cardiac tissue with OM was lowered significantly, whereas IL-10 was still maintained at a higher level in drug-treatment group (showed in Table III).

Discussion

Hypertension has the particular features of being sufficiently common to represent a public health concern, yet its morbidity is still showing a tendency of rising every year[22]. In the study,

Table I. The ratio of left ventricle mass to body weight of three groups ($\bar{x} \pm s$).

Group	N	LVM/BW
SO	7	0.002839 ± 0.000239
MC	8	0.004301 ± 0.000652*
OM	8	0.002937 ± 0.000250**

*vs. SO: $p < 0.0001$: **vs. MC: $p < 0.001$.

Table II. Theserum levels of IL-6 and IL-10 ($\bar{x} \pm s$).

Group	N	IL-6 (pg/ml)	IL-10 (pg/ml)
SO	7	52.70 ± 9.633	75.16 ± 4.824
MC	8	88.54 ± 7.418*	102.59 ± 9.797*
OM	8	75.23 ± 7.289**	96.56 ± 7.244*,Δ

*vs. SO: $p < 0.0001$; **vs. MC: $p < 0.001$; Δvs. MC: $p > 0.05$.

we compared the LVM/BW ratios in three groups (SO, MC and OM). The important novel finding of the present study is that OM reverses LVH and reduces the IL-6 levels in the renovascular hypertensive rats. These data demonstrate that OM had significant effects on attenuating LVH and the levels of IL-6 in serum and cardiac tissue with OM was lowered significantly, but IL-10 levels in this animal model was not statistically significant.

According to our findings, it can be deduced that the levels of IL-6 was related to LVH and hypertension. The common link between IL-6 and hypertension was also showed in other studies. For instance, -174G/C promoter polymorphism of IL-6 is associated with hypertension and LVH in dialysis patients[23]. IL-6 was correlated with the development of hypertension and its complications. A previous study[24] showed that IL-6 levels were increased in hypertensive despite good blood pressure control. Moreover, IL-6 can cause cardiac hypertrophy through the IL-6 signal transducing receptor component-glycoprotein 130[25], and concentric hypertrophy[26,27]. It is critical to lower the levels of pro-inflammatory cytokines such as IL-6 for the therapy of hypertension.

Our work revealed that IL-10 levels in renovascular hypertensive rats were not statistically significant. IL-10 has potent inhibitory effects on pro-inflammatory cytokine synthesis produced by activating monocytic cells, and various studies have manifested its profits to our body. For instance, a research by Didion et al[28] shows endogenous IL-10 can limit Angiotensin II-mediated oxidative stress and vascular dysfunction both in vitro and in vivo, suggest that IL-10 may militate the protective effects within the vessel wall. Another study[29] indicate interleukin-10 overexpression in macrophages maybe suppress atherosclerosis in hyperlipidemic mice. Elevating the levels of IL-10 may be a target for anti-inflammatory therapy in hypertension.

Table III. Thelevels of IL-6 and IL-10 in cardiac tissue ($\bar{x} \pm s$).

Group	N	IL-6 (pg/ml)	IL-10 (pg/ml)
SO	7	43.64 ± 3.563	87.67 ± 8.247
MC	8	77.63 ± 9.675*	116.36 ± 14.653*
OM	8	60.46 ± 6.452**	111.68 ± 9.033*,Δ

*vs. SO: $p < 0.001$; **vs. MC: $p < 0.001$; Δvs. MC: $p > 0.05$.

This study demonstrated that ligating the abdominal aorta in healthy Wistar rats caused renovascular hypertension. However, olmesartan could decrease the serum and cardiac tissue levels of IL-6 significantly, it could maintain the serum and cardiac tissue levels of IL-10 at the same time. LVH is an independent cardiovascular risk factor, there is evidence that the most effective antihypertensive drug for LVH regression is the renin-angiotensin system inhibitor[7]. As discussed elsewhere, suppress the influence of angiotensin II by angiotensin II receptor blockers may reduce or potentially reverse cardiovascular diseases, such as atherosclerosis and LVH[30]. Angiotensin II, the active product of the renin-angiotensin system, is a hormonal regulator of cardiovascular function and electrolyte metabolism[31], and a crucial factor in the development of hypertension and its complications. Various angiotensins II receptor blockers are widely used for the treatment of hypertension in recent years. It is clear that angiotensin II is decreased by the potent hypotensive effects of olmesartan[32]. Olmesartan is able to reduce blood pressure of hypertensive patients in long-term administration[16], as well as serum levels of IL-6 after 6 weeks of therapy[33].

Conclusions

Olmesartan Medoxomil, an angiotensin II receptor blocker, has a preferable anti-inflammatory effect. It completely reversed left ventricle hypertrophy and reduced IL-6 levels in both the serum and cardiac tissue. A large-scale trial is needed to verify these positive effects as our study including small number of rats.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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