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The Effect of Telmisartan on Bone Morphogenetic Protein-7 (BMP-7) Expression in the Kidney of 8% Sodium Chloride-Treated Rats

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Abstract

Excessive salt consumption is one of the hypertension factor leads to kidney disease, while telmisartan is one of antihypertensive drugs used in the therapy. Telmisartan not only blocks angiotensin receptor leads to the decrease of blood pressure, but it also activates peroxisome proliferator activated receptor gamma (PPAR-γ), inhibits transforming growth expression factor of beta-1 (TGFβ-1) and increases bone morphogenetic protein-7 (BMP-7). Whether telmisartan increases BMP-7 expression of excessive NaCl–induced Wistar rats are studied in this experiment. Twenty five male Wistars 2.5-3 months of age and 100-150 g BW rats were used in this research. They were grouped into 5, each consists of 5 rats. Group I (G I) as first negative control did not receive NaCl and telmisartan. G II as second negative control received NaCl but not telmisartan. G III, IV and V received NaCl and telmisartan 3, 6 and 12 mg/kg BW. The treatments were given every day within 8 weeks. At the day of 56 all rats were sacrificed by mean of neck dislocation and operated to take the kidney. The expression of BMP-7 was measured by immunohistochemistry technic. Data were expressed as mean ± standard deviation. They were analyzed by parametric (ANOVA) or nonparametric (Kruskal-Wallis) test. A value of $p<0.05$ was considered statistically significant. The results showed that intraglomerular and extraglomerular BMP-7 protein expression were higher in telmisartan-treated Wistar rats group than negative control group ($p<0.05$). In conclusion, intraglomerular and extraglomerular BMP-7 protein expression were higher in 8% sodium chloride-induced and telmisartan-treated male Wistar rats than the items of negative control group.

Keywords: NaCl; Telmisartan; BMP-7

Introduction

In 2010, non-communicable diseases (NCD) caused 36 million deaths every year-63% of all deaths globally. Three major NCDs are cancers, cardiovascular and diabetes [1].

Essential hypertension is the main society health problem. In 2005, approximately 1 billion people (14%) globally had hypertension. Hypertension is the main risk factor for cardiovascular, cerebrovascular and kidney diseases that related to the fibrosis occurrence in several organs, such as heart, kidney, liver and cardiovascular [2,3].

Previous research on animal model, it showed that 8% sodium chloride could induce hypertension on rats [4]. The mechanism is thought to me via the activation of angiotensin II by sodium in *aldosterone→endogenousoabain* (EO) [5]. Angiotensin II stimulates vasoconstriction and adrenal gland to secrete aldosterone leads to the stimulatation distal tubulus sodium and water reabsorption [6,7]. Moreover, angiotensin II induces the change of fibroblast to miofibroblast by pathway of *transforming growth factor-beta1* (TGF-β1). Myofibroblast produces exaggerated extracelluer matrix (ECM), therefore, ECM accumulates in tubulointerstitial area [8]. TGF-β1 is a cytokines that play a role in fibrosis formation through the decrease of BMP-expression in the in the epithelial of proximal tubulus during kidney fibrosis [9]. Bramlage et al. stated that inhibition of fibrosis pathway via TGF-β1 may increase BMP-7 gene expression in hypertensive nephrosclerosis, tubulointerstitial fibrosis and diabetic nephropathy [10]. Therefore BMP-7 plays a role as antifibrotic for kidney [11]. According to Zeisberget al. that BMP-7 found mostly in kidney, cartilage and bone [12] and may potentially explored as biomarker for the effectiveness and new potential effects.

Telmisartan not only blocks angiotensin receptor, but also plays a role as agonist partial peroxisome proliferator activated receptor-γ (PPAR-γ), so that it activates PPAR- γ [13,14]. The activation causes PPAR-γ forms heterodimer with *retinoid X receptors* (RXRs) so that corepressor is formed that can inhibit gene expression of TGF-β1 [15].

Materials and Methods

Twenty five male Wistars 2.5-3 months of age and 100 – 150 g BW rats were used in this experiment. They were maintained in individual pen and given feed pellet and drinking water adequately, placed in room temperature 20-24°C, dark-bright cycle for 12 hours. Before treatment, animal model was acclimatized for 7 days. They were grouped into 5 each consists of 5 rats. Group I (G I) as first negative control did not receive NaCl or telmisartan. G II as second negative control recived NaCl but not telmisartan. G III, IV and V received NaCl and telmisartan 3, 6 and 12 mg/kg BW. The treatments were given every day for 8 weeks. At the day of 56 all rats were sacrificed by dislocating their necks and operating to take the kidney [16,17].

Forty mg telmisartan tablet was crushed mortally and then add water until 40 mL. Its suspension was taken by syringe suitable to rats dosage that have been determined to be entered directly to the rats' stomach [18]. BMP-7 protein expression was measured by immunohistochemistry technic and determined by measuring the area of stained tissue within a given field. The area stained was calculated by image J software as percentage of the total area within a field [4,19-22].

The data are expressed as mean ± standard deviation and analyzed using parametric (ANOVA) or nonparametric (Kruskal-Wallis) test. A value of $p<0.05$ was considered statistically significant.

Results

Telmisartan Effect to BMP-7 Protein Expression in Kidney of 8% Sodium Chloride- Induced Wistar rats.

Intraglomerular and extraglomerular BMP-7 protein expression were higher in kidney of telmisartan-induced Wistar rats than negative control. According to Tables 1 and 2 and Figure 1 that intraglomerular and extraglomerular BMP-7 protein expression of group III, IV and V>group I and II.

Group	BMP-7 protein expression (%) of rat Number					Mean ± SD	p
	1	2	3	4	5		
I	19.8	23.8	24.2	0.38	20.4	17.71 ± 9.8	0.018*
II	22.5	29.3	32.9	19.5	14.4	23.72 ± 7.4	
III	26.8	32.1	27.4	22.1	18.1	25.3 ± 5.3	
IV	28.1	18.4	34.9	15.6	37.7	26.94 ± 9.7	
V	38.2	45.9	46.1	56.1	33.9	44.04 ± 8.5	
*significant difference of mean in Wistar rat group ($p<0.05$)							

Table 1: IntraglomerulerBMP-7 protein expression (group I and II=negative control; group III, IV and V=8% NaCl+telmisartan 3, 6 and 12 mg/kg BW).

Group	BMP-7 protein expression (%) of rat Number					Mean ± SD	p
	1	2	3	4	5		
I	36.1	53.6	54.0	6.25	57.9	41.57 ± 21.4	0.025*
II	54.2	48.9	42.9	60.4	21.3	45.54 ± 15.01	
III	49.6	41	53.9	55.2	39	47.74 ± 7.3	
IV	56.7	49.9	35.6	48.4	46.2	47.36 ± 7.65	
V	59.4	63.4	63.2	63.5	68.4	63.58 ± 3.19	
*Significant difference of mean inWistar rat group ($p<0.05$)							

Table 2: ExtraglomerulerBMP-7 protein expression (group I and II=negative control; group III, IV and V=8% NaCl+telmisartan 3, 6 and 12 mg/kg BW).

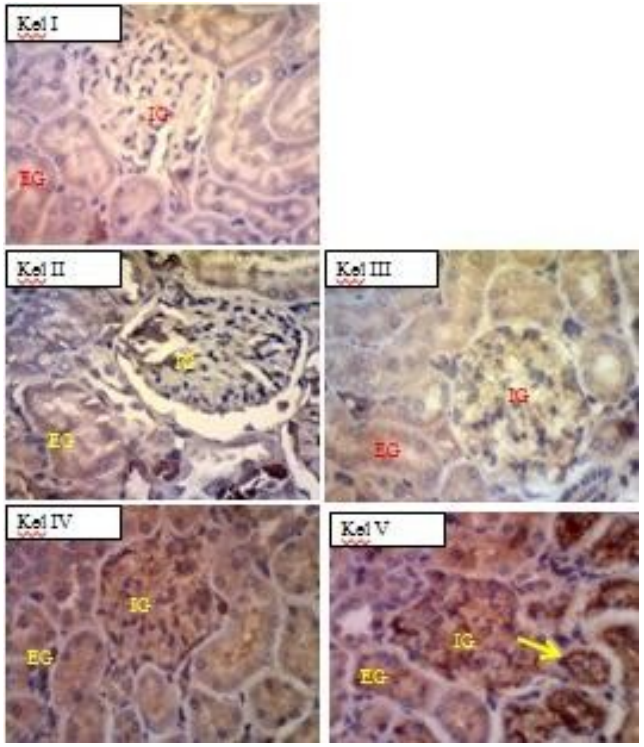

Figure 1: Microscopic picture of kidney slide in 400× magnification for group I, II, III, IV and V that have been stained by immunohistochemistry (brown color → shows cells express BMP-7 protein in cytoplasma area). IG=intraglomerular, EG=extraglomerular.

Discussion and Conclusion

Cox et al. expressed salt can induce fibrosis on heart, kidney and cardiovascular that be proved from two separated cohort studies in human population [3]. Yu et al. also revealed salt induces fibrosis in kidney, left ventricle and intramioacrdial artery of rats. Kidney fibrosis causesend stage renal disease (ESRD) which worsen the kidney condition [4]. Fibrosis induction in kidney increases blood pressure and induces chronic and acute kidney disease.

In chronic and acute kidney disease, the expression of BMP-7 is decreased; meanwhile TGF-β1 expression is increased. Physiology restoration of BMP-7 expression in kidney was associated to kidney structure regeneration. Therefore, TGF- β1 playsa role as pathogenic molecule; meanwhile BMP-7 can be protective agent [23].

TGF-β1 signaling is affected by Posphorilation-Smad2 that be induced by the binding between TGF-β1 and its receptor. In contrast, Smad6 and bone morphogenetic protein receptor type-I (BMPR-1) prevent posphorilation-Smad2 and cause disintegration of Smad2 complex [24]. In addition, Zhong et al. explained that rhBMP-7 can stop Smad-2/-3 nuclear translocation in primary hepatic stellate cells (PHSCs) and hepatocyte, so that liver fibrosis doesn't be formed [25]. Smad-2/-3 nuclear translocation mechanism in liver and kidney areactivated by TGF-β1. Therefore, the increase of BMP-7 expression prevents kidney fibrosis with disintegration of Smad2 complex and stopping of Smad-2/-3 nuclear translocation mechanism.

Clinical study of telmisartan is developed to know the effect of telmisartan on patients' hypertension with kidney, hearth and vascular disease [26]. Telmisartan functions blocking angiotensin receptor and as agonist partial ligand of PPAR-γ so that PPAR-γ formed heterodimerisation with RXRs which induces inhibitor corepressor formation of TGF-β1 gene expression. The inhibition of TGF-β1 increases the expression of BMP-7 protein.

Finally, telmisartan reduces the expression of TGF-β1 and increase BMP-7 expression.

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