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Effects of Valsartan and Telmisartan on the LungTissue Histology in Sensitized Rats

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Abstract The renin-angiotensin system (RAS)was potentially implicated in the pathogenesis of pulmonary disorders through its involvement in inducing pro-inflammatory mediators in the lung tissues. The present study evaluates the effects of the angiotensin receptor blockers (ARBs), telmisartan and valsartan, on the histological changes of lung tissues in sensitized rats. Twenty-fourWister female rats were randomly divided into four groups: A, negative control; B, valsartan-treated group; C, telmisartan-treated group and D, positive control. The rats in the groups B-D were sensitized and challenged with ovalbumin (OVA). Group A rats were sensitized and challenged with normal saline. Rats from groups B and C were treated with either valsartan or telmisartan (5mg/kg/day), respectively. The effects of administered ARBs on lung tissue structures were histologically evaluated. Treatment with telmisartan significantly attenuates the inflammatory and the hyper-proliferative changes in lung tissue after OVA-challenge, while valsartan did not show such effect. In conclusion, telmisartan demonstrates anti-inflammatory and anti-proliferative activities in sensitized rats, while valsartan lacks these effects.

Keywords: *telmisartan, valsartan, sensitization, inflammation, lung*

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1. Introduction

Airway disorders associated with persistent inflammation, such as chronic obstructive pulmonary disease (COPD) and asthma and recognized as chronic conditions; they are influenced by a combination of environmental, genetic and epigenetic components [1]. Inflammation of the airways plays a central role in the pathogenesis of asthma and COPD, and the clinical investigations showed a correlation between the presence of activated inflammatory cells (neutrophils, mast cells, and eosinophils), histological changes in pulmonary tissue with the development of airways hyper-reactivity [2]. Meanwhile, ongoing airway inflammation and associated airway remodeling played a pivotal role in the development of airway hyper-responsiveness and airflow limitations [3]. It was found that repeated allergen inhalation increased airway smooth muscle mass, pulmonary contractile protein expression and the contractility of tracheal smooth muscle; all indicative of airway smooth muscle remodeling [4]. A local renin-angiotensin system (RAS) exists in many human tissues including the lung, and angiotensin II (AgII) receptors are expressed in the pulmonary tissues [5]. Animal studies have indicated that Ag II receptor 1 (AgIIR1) is involved in Ang II effects including bronchoconstriction in guinea pigs [6]. It stimulates the release of pro-inflammatory cytokines, activates nuclear factor kappa B (NF-kB), increases oxidant stress, suppress nitric oxide synthesis and behave as an inflammatory molecule [4]. It also induces inflammation through the production of reactive oxygen species, adhesion molecules, and inflammatory cytokines such as chemo-attractant protein-1 (MCP-1). MCP-1 acts as a central mediator of inflammatory response in hypertensive vascular disease [7]. Ag II also induces cyclooxygenase-2 (COX-2) synthesis and release [8]. Chronic inflammation of the central and peripheral airways was recognized as a central feature of many pulmonary disorders, including asthma and COPD and mostly associated with lung remodeling, parenchymal destruction and the development of emphysema [9]. The RAS was potentially implicated in the pathogenesis of pulmonary disorders through its involvement in inducing pro-inflammatory mediators in the lung tissues [10]. Pulmonary fibrosis is relevant to the pathogenesis of inflammatory lung diseases in two ways; first, fibrosis, whichis a component of airway remodeling in asthma COPD [11]; second, it is now well recognized that a proportion of COPD patients have a syndrome of combined pulmonary fibrosis and emphysema with distinct clinical features [12]. Evidence for the involvement of pulmonary RAS in lung fibrosis comes from studies of broncho-alveolar lavage fluid from patients with inflammatory lung disorders, showing elevated angiotensin converting enzyme (ACE) levels [13]. In lung biopsies taken from patients with idiopathic lung

fibrosis, Li et al. [14] found an increased level of angiotensinogen protein and mRNA, which localized to areas of epithelial apoptosis and myofibroblast foci. These findings are supportedby the work of Raupach et al. [15], who investigated the effects of the ARB AngII receptor blocker (ARB) irbesartan on an emphysema mouse model, finding benefits in histological emphysema severity, lung compliance and exercise capacity following treatment. The present study was designed to evaluate the effect of telmisartan and valsartanon the histology of pulmonary tissues in the airways of sensitized rats.

2. Materials and Methods

Twenty-four Wister albino female rats (3 weeks old) weighing 180-250 g, obtained from the College of Pharmacy/University of Baghdad, were housed in the animal house, College of Pharmacy, University of Basra; they were maintained on normal conditions of temperature, humidity and light/dark cycle. They fed standard rodent pellet diet and they had free access to water. The local Research Ethics Committee in College of Pharmacy, University of Baghdad, approved the research protocol. The animals randomly allocated into four groups (each of 6 rats) according to the type of treatment; group A, treated with distilled water (negative control); group B, treated with valsartan (5mg/kg/day); group C, treated with telmisartan (5mg/kg/day); group D, treated with distilled water (0.5 ml/day) and kept as positive control. Both drugs and the vehicle (distilled water) administered orally as single daily doses using gavage tube.According tothe methods of Xue et al [16], the rats in the positive control group and ARBs-treated groups (B-D) were sensitized by intraperitoneal injections on days 0 and 7 with 100 mg ovalbumin (OVA) and 100 mg $Al(OH)_3$ in 1 ml saline. On day 15, the rats were challenged with inhaled nebulized 1% OVA for 30 minutes, every other day for 30 days. Sixty minutes prior to OVA exposure, the rats in groups B-D were givenorallyvalsartan, telmisartan or distilled water, respectively. The rats in the negative control group were sensitized and challenged with 0.9% saline, every other day for 30 days. Challenges took place in a chamber (20 cm × 30 cm × 40 cm) with free-breathing animals. After challenging the rats, they were killed by intraperitoneal injection of 50mg/kg phenobarbitone sodium and their lungs were extracted, fixed in 10% neutral buffered formalin and embedded in conventional paraffin. Sections were prepared and stained with Hematoxyline and Eosin (H&E) for structural and morphometric evaluation. For these measurements, photomicrographs of three fields from each section containing airways were taken using a digital camera (JVC TK-890-E; JVC, Yokohama, Japan) fitted to an Olympus BH-2 RFCA microscope (Olympus Optical Co. Ltd, Tokyo, Japan) [17]; thicknesses were measured using a calibrated micrometric analyzer at 8 different points on 2 to 3 different airways.

3. Statistical Analysis

Data were expressed as mean ± SD. The Statistical significance of the differences between various groups was determined by Post-hoc test (LSD alpha 0.05) and one-way analysis of variance (ANOVA) using SPSS for Windows. Differences were considered statically significant for p-value< 0.05.

4. Results

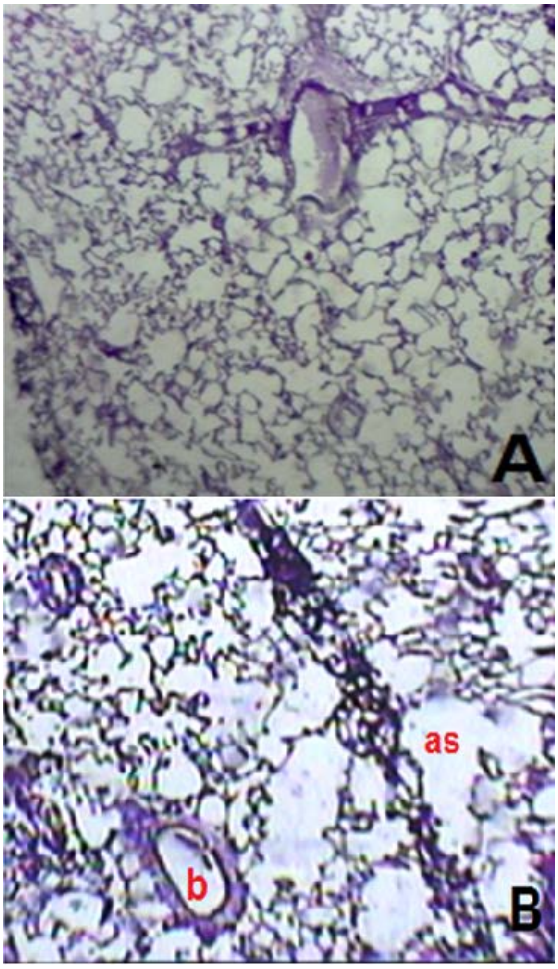

Figure 1. Sections of lung tissue fromnegative control group stained with H&E (A, 4X; B, 10X).Clear bronchioles (b) and alveolar sac (as)without infiltration of inflammatory cell

Histopathological study of lung tissue in negative control group revealed the alveolar sac and bronchioles with normal epithelium (Figure 1). In sensitized rats (group D), the sections showed increased accumulation of inflammatory cells that occluded the bronchioles and the alveolar sac, with thickness of alveolar smooth muscle and trachea (Figure 2). In Figure 3, treatment of sensitized rats with telmisartan clearly shows improved histological appearance, decreases in infiltration with inflammatory cells, and relatively clear bronchial and alveolar sacs with remarkable decrease in the thickness of alveolar epithelium and tracheal smooth muscles. However, no remarkable improvement reported in lung tissue sections from group B (valsartan-treated) animals, where the histological appearance is comparable to that shown in positive control (group D) (Figure 4). As shown in Table 1, the mean thickness of alveolar smooth muscle in positive control group was significantly greater than that reported in negative control (118%, P<0.05). Treatment with valsartan shows very small decrease in thickness which is comparable to that reported in positive control group and

significantly higher than that reported in negative control group (103%, $P<0.05$). Meanwhile, treatment with telmisartan significantly decreases the smooth muscle thickness compared with positive control group (46%) and that reported in valsartan-treated group (39%); this value was found comparable to that reported in negative control group ($P>0.05$). In Table 2, the mean thickness of trachea in positive control group was significantly higher than that reported in negative control (77.4%, $P<0.05$). Treatment with valsartan shows very small decrease in thickness of trachea in sensitized rats, which is comparable ($P>0.05$) to that reported in positive control group and significantly higher than that reported in negative control group (60.5%, $P<0.05$). Meanwhile, treatment with telmisartan significantly decreases the thickness of trachea compared with positive control group (36.5%) and that reported in valsartan-treated group (30%); this value was found comparable to that reported in negative control group ($P>0.05$).

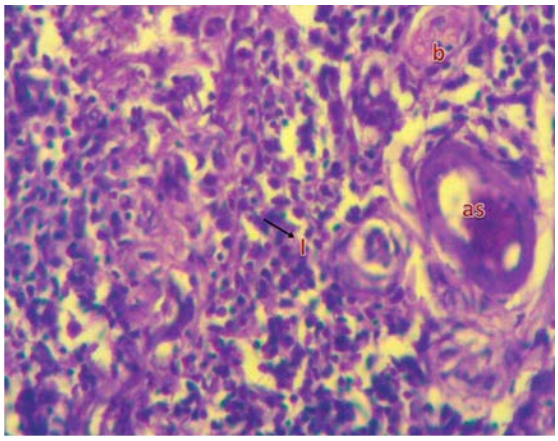

Figure 2. Sections of lung tissue from positive control groups stained with H&E (40X); the section was filled with inflammatory cell (I),bronchioles(b) and alveolar sac (as)were filled with exudate and inflammatory cell

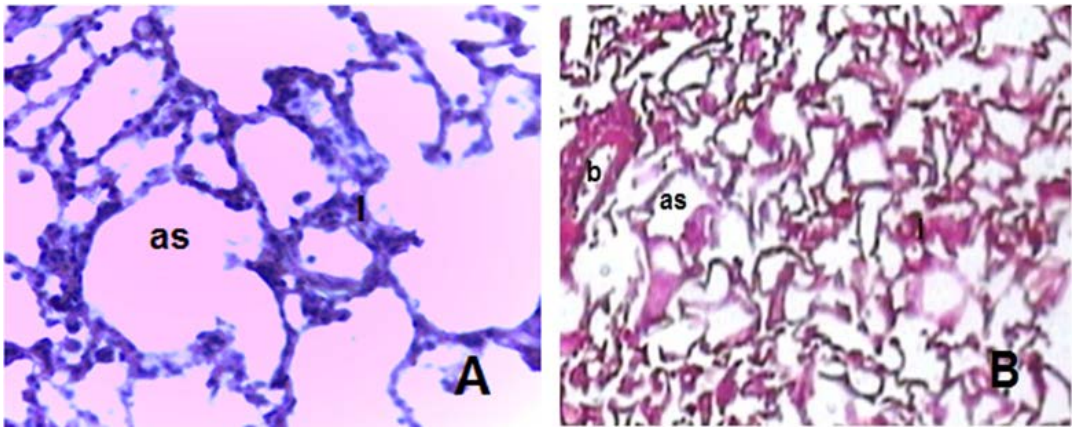

Figure 3.Sections of lung tissue from telmisartan-treated group stained with H&E (A, 40X; B, 10X);few inflammatory cell (I),the bronchioles(b) and alveolar sac (as)were nearly clear

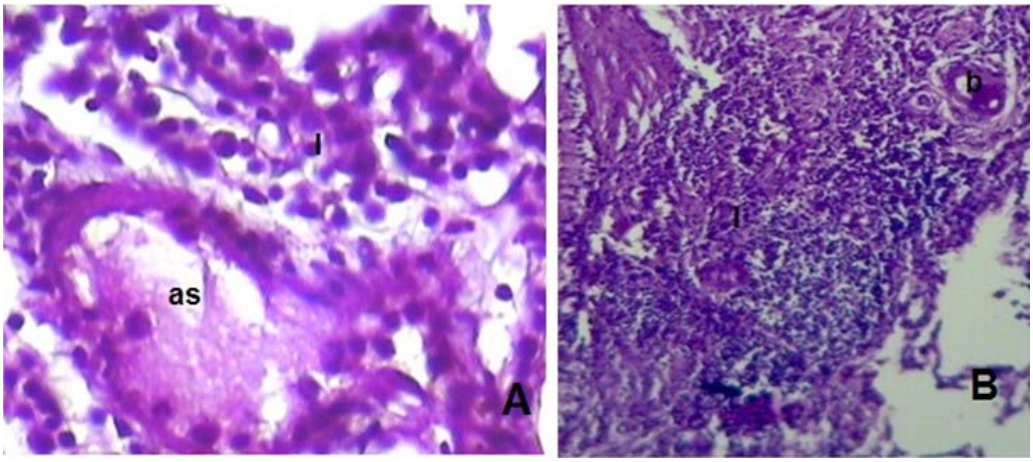

Figure 4.Sections of lung tissue fromvalsartan-treatedgroup stained with H&E (A, 40X; B,10X); the section was filled with inflammatory cells (I),bronchioles(b) and alveolar sac (as)were filled with inflammatory exudate

Table 1.Effect of telmisartan and valsartan on thickness of alveolar smooth muscle in sensitized rats

Treatment groups	Mean thickness of alveolar smooth muscle (μm)
A (negative control)	6.1±0.54[a]
B (5mg/kg telmisartan)	7.6 ±0.30[a]
C (5mg/kg valsartan)	12.4±1.63[b]
D (positive control)	13.3±2.08[b]

Data are expressed as mean±SD; n=6 animals in each group; values with non-identical superscripts (a, b) are significantly different ($P<0.05$).

Table 2.Effect of treatment with telmisartan and valsartan on thickness of trachea in sensitized rats

Treatment groups	Mean thickness of trachea (μm)
A (negative control)	59.2±4.0[a]
B (5mg/kg telmisartan)	66.7±2.5[a]
C (5mg/kg valsartan)	95.0±5.8[b]
D (positive control)	105.0±3.7[b]

Data are expressed as mean±SD; n=6 animals in each group; values with non-identical superscripts (a,b) are significantly different (P<0.05).

5. Discussion

Repeated exposure of pulmonary tissues to sensitizing agents results in different degrees of airway remodeling. In addition to the recruitment of many types of inflammatory cells to the pulmonary tissues, airway remodeling also involves proliferation of smooth muscle cells, shading of epithelium and proliferation of the extracellular matrix, which is mostly attributed to the over expression of many growth factors including TGF-β1 [18]. The present study confirms that repeated sensitization results in pulmonary tissue injury including proliferation of smooth muscle cells in the trachea and alveoli, as evidenced by the stained tissue sections and morphometric measurements. Although AngII can act as a weak bronchoconstrictor throughits AT1R, it can act synergistically with endothelin-1 to produce more powerful contractions in bronchial bovine smooth muscles [19,20]. AngII can activate phospholipase A2 and the release of arachidonic acid from membrane phospholipids [21]. Arachidonic acid is then converted into thromboxane A2 by the action of cyclooxygenase and into leukotrienes by lipoxygenase [22]. The results of the present study was in tune with the previously mentioned one, where typical inflammatory response was evident in the tissue sections, in addition to the remodeling of the airways manifested as increased thickness of the smooth muscle layers in both trachea and alveoli. Airway remodeling is an integral part of bronchial hyper responsiveness, since it distorts and alters permanently the structure and caliber of the bronchi. These changes occur in response to persistent inflammation and include subepithelial fibrosis, hyperplasia ofmucus glands, myofibroblast and smooth muscle proliferation andangiogenesis [23,24]. The present study has shown that telmisartan (5mg/kg/day) prevents and/or relieves allergen-induced inflammatory cells accumulation and excessive proliferation in lungs of ovalbumin-challenged rats, while valsartan do not show such type of activity when administered in equivalent doses to telmisartan for the same purpose. The anti-inflammatory effect of telmisartan in this model was reported for the first time; however, such anti-inflammatory activity was previously reported in other models of inflammation [25]. Although previous studies demonstrate the effectiveness of valsartan as anti-inflammatory agent in experimentally-induced pulmonary inflammation [26,27], the present study fails to report such activity; this may be attributed to insufficient doses utilized there. These results have suggested that blockade of Ang II receptors may be animportant treatment option in the management of chronicasthma. Moreover, the predominant effect of telmisartan reported in the present study may be attributed to other mechanisms specifically utilized by telmisartan, including effective PPAR-γ activation [28], while valsartan lacks such activity [29]. According to the outcome of the present study, the anti-inflammatory activity of telmisartan may not be attributed to the Ag II receptor blockade only, and other mechanisms might be involved including PPAR-γ agonist activity. Further studies are highly suggested to compare the activities of different ARB analogues in this model.

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